

1 IN THE UNITED STATES DISTRICT COURT

2 IN AND FOR THE DISTRICT OF DELAWARE

3 - - -

4 RESEARCH FOUNDATION OF STATE

UNIVERSITY OF NEW YORK, et al., : CIVIL ACTION

5 Plaintiffs, :

6 v. :

7 MYLAN PHARMACEUTICALS, INC., :

8 Defendant. :

NO. 09-184-LPS

9 -----
MYLAN PHARMACEUTICALS, INC.,

10 Plaintiff, :

11 v. :

12 GALDERMA LABORATORIES, INC., :

GALDERMA LABORATORIES, L.P., and :

13 SUPERNUS PHARMACEUTICALS, INC., : NO. 10-892-LPS

14 Defendants.

- - -

15
16 Wilmington, Delaware
Wednesday, July 6, 2011
BENCH TRIAL - VOLUME B

18 - - -

19 BEFORE: HONORABLE **LEONARD P. STARK**, U.S.D.C.J.

20 APPEARANCES:

- - -

21 MORRIS NICHOLS ARSHT & TUNNELL, LLP

22 BY: JACK B. BLUMENFELD, ESQ.

23 and

24
25 Brian P. Gaffigan
Valerie Gunning
Official Court Reporters

1 APPEARANCES (Continued):

2
3 PAUL HASTING JANOFSKY & WALKER, LLP
4 BY: GERALD J. FLATTMANN, ESQ.,
5 CHRISTINE WILLGOOS, ESQ.,
6 JOSEPH M. O'MALLEY, JR., ESQ., and
7 MELANIE R. RUPERT, ESQ.
8 (New York, New York)

9
10 Counsel for Research Foundation of
11 State University of New York, Galderma
12 Laboratories, Inc., New York University,
13 Galderma Laboratories, L.P., and
14 Supernus Pharmaceuticals, Inc.

15
16 POTTER, ANDERSON & CORROON, LLP
17 BY: RICHARD L. HORWITZ, ESQ.

18 and

19 WILSON SONSINI GOODRICH & ROSATI, PC
20 BY: DAVID S. STEUER, ESQ.,
21 MATTHEW R. REED, ESQ., and
22 KIRIN K. GILL, ESQ.
23 (Palo Alto, California)

24 and

25 WILSON SONSINI GOODRICH & ROSATI, PC
BY: TUNG-ON KONG, ESQ.
(San Francisco, California)

and

WILSON SONSINI GOODRICH & ROSATI, PC
BY: LORI P. WESTIN, ESQ.,
(San Diego, California)

Counsel on behalf of
Mylan Pharmaceuticals, Inc.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

- oOo -

P R O C E E D I N G S

(REPORTER'S NOTE: The following trial proceedings was held in open court, beginning at 8:31 a.m.)

THE COURT: Good morning, everyone.

(The attorneys respond, "good morning, your Honor.")

THE COURT: Are there any issues the parties wish to take up before we begin for the day?

MR. FLATTMANN: Yes, your Honor. We have a number of evidentiary objections to the witnesses Mylan intends to call today.

THE COURT: Let's have you come to the podium and present your objection.

MR. FLATTMANN: Thank you, your Honor.

I'd first like to address the evidentiary issues proposed testimony of Dr. Gilchrest today. They are essentially in two parts, your Honor.

First, they seek the admission of two declarations. One is the declaration of Dr. Feldman, and I'm talking about the declaration aside and apart from the patient record which we've stipulated could be admitted.

THE COURT: Mr. Reed has immediately risen.

MR. REED: Let me clarify we're not going to seek to admit the declaration of Dr. Feldman.

1 MR. FLATTMANN: That solves that problem, your
2 Honor.

3 THE COURT: Okay. All right.

4 MR. FLATTMANN: The second is the declaration of
5 Dr. Jones which is on Dr. Gilchrest's list of intended
6 exhibits again.

7 THE COURT: He has risen again.

8 MR. REED: This one I will take credit for. I
9 apologize. We're not seeking that to be presented.

10 THE COURT: You are two for two.

11 MR. FLATTMANN: That was easy.

12 THE COURT: Yes, I hope they're all that easy.

13 MR. FLATTMANN: The other issues might not be
14 quite as easy. They relate to the addition of art to the
15 list of exhibits to be used with Dr. Gilchrest; in fact,
16 eight references that are not on their revised and reduced
17 section 282 notice that was served before the trial.

18 We have met and conferred. They have
19 represented that they only seek to use these as so-called
20 state of the art. Your Honor, I think that is a distinction
21 without a difference here, particularly in light of the
22 Gilchrest proposed demonstratives which indicate that they
23 intend to combine the so-called state of the art with the
24 references that are actually on the 282 notice in order to
25 make arguments in claim chart fashion, for instance, as to

1 which elements are met by the claims. So that is
2 essentially using this new state of the art as prior art
3 that is not on the 282 list once again revising piles of art
4 they're relying on in an attempt to invalidate, and I think
5 that is improper, and we object to the use of that and the
6 combinations.

7 THE COURT: Have you seen these eight references
8 previously or they're completely new to you?

9 MR. FLATTMANN: We have seen these references.
10 I believe we have seen them previously. At least, many of
11 them.

12 THE COURT: Were there other issues?

13 MR. FLATTMANN: Well, there will be objections
14 to the same exhibits and to the same combinations on the
15 grounds that they're outside the scope of the expert report;
16 and we'll raise those in accordance with the Court's
17 procedure.

18 THE COURT: And remind me who Dr. Gilchrest is.

19 MR. FLATTMANN: Dr. Gilchrest is their expert
20 with regard to the validity issues concerning the Ashley
21 patent.

22 THE COURT: Thank you.

23 MR. FLATTMANN: Well, your Honor, we do have
24 additional evidentiary issues going to Dr. Stafford and
25 Dr. Robbins that would be addressed by my colleagues, if

1 that is okay.

2 THE COURT: Let's deal with the Dr. Gilchrest
3 objection first, and then we'll move on to the other
4 witnesses.

5 MR. STEUER: Okay. So, David Steuer from Mylan.

6 The references, of course, have all been -- they
7 were all in Dr. Gilchrest's report. He was cross-examined
8 on them. The actual proceeding that leads us to this
9 objection is when we were preparing a narrowed list of
10 references, Galderma took the position that our list was too
11 long; and so we said, well, many of these are being used as
12 background art, to show the state of the knowledge of a
13 person of ordinary skill in the art, what was known to
14 dermatologists. And they said, well, that is okay. Take
15 those out of your list since they are not anticipation,
16 which they are not. They are used to show the knowledge of
17 a person of ordinary skill in the art.

18 So at their request, we did that, but we -- I
19 won't say we anticipated this issue, but in our narrowed
20 list, we said -- and these were all references that were on
21 the list that we gave them, and then we took them off. We
22 took them off because they said, well, they're not
23 anticipatory so you shouldn't list them.

24 When we sent it in, we had this statement that
25 said: Mylan provides its narrowed list with the parties'

1 explicit understanding that Mylan will be presenting at
2 trial evidence regarding additional references previously
3 listed in its expert reports as background materials showing
4 the state of knowledge in the art and with plaintiffs'
5 agreement that plaintiffs will not object to the
6 introduction of that evidence based on the fact that such
7 references do not appear on this narrow list.

8 That is exactly what is happening is they're
9 objecting to us because it wasn't on the narrowed list, and
10 that is what we worried about, but counsel agreed that this
11 objection would not be proper.

12 THE COURT: Are you going to argue that these
13 eight state of the art references provide a basis to
14 invalidate the Ashley patents?

15 MR. STEUER: Only as we describe here, which is
16 dermatologists are aware of certain facts as dermatologists,
17 and this shows what the state of the art of general
18 knowledge is. These aren't anticipatory documents.

19 THE COURT: Are they documents you are using to
20 ask the Court to invalidate these patents as obvious?

21 MR. STEUER: I will say to the extent they
22 contribute to what is within the knowledge of a person of
23 ordinary skill in the art, they would provide additional
24 bases for invalidating the art.

25 THE COURT: Does Dr. Gilchrest intend to testify

1 that explicitly that some combination of disclosures in the
2 some or all of these references combined with other art
3 invalidates the patents?

4 MR. STEUER: What I believe that Dr. Gilchrest
5 will say, she will say, for example, for a particular
6 limitation, this refers to, for example, a dose of
7 tetracycline. Persons of skill in the art know that
8 tetracycline of that dose is not antibacterial.

9 How do we prove people of skill in the art know
10 that? Well, because there have been many publications on
11 that. There are many publications on that part which these
12 references reference. We see this as background material to
13 explain what is known in the art; and, of course, that is
14 what these were presented as in Dr. Gilchrest's expert
15 report.

16 THE COURT: Okay. Is there anything else on
17 that from you, Mr. Steuer.

18 MR. STEUER: That's it, your Honor.

19 THE COURT: Mr. Flattmann, you can respond.

20 MR. FLATTMANN: Your Honor, counsel really
21 hedged what she was going to say or not going to say. This
22 is just an obviousness argument, a classic obviousness
23 argument disguised as so-called state of the art.

24 If you go to the demonstrative slides
25 Dr. Gilchrest intends to use -- and I know they will be

1 before the Court soon. DDX-241, for instance, will say that
2 low dose tetracycline did not inhibit bacterial growth in
3 sebaceous glands, and she cites the Cunliffe as evidence of
4 that.

5 And two slides later, on DDX-243, she says the
6 claims are anticipated by Murphy; and under Murphy, which
7 says nothing about bacterial flora, and she will admit that,
8 she says Murphy administered oxytetracycline in a dose that
9 will not affect bacterial flora in sebaceous glands.

10 So she is clearly going to be combining the
11 teachings of these references in an attempt to invalidate,
12 and that's in appropriate because they're not on the 282
13 list. And they're are other examples.

14 MR. STEUER: May I respond, your Honor?

15 THE COURT: Just very briefly.

16 MR. STEUER: Very briefly.

17 These were all on the 282 list; and at the
18 request of Galderma, we put it down because they said it was
19 because these documents, in and of themselves, anticipate.

20 So I understand, from Mr. Flattmann's comments,
21 that he feels that they've been a bit surprised, but I too
22 am surprised because this was exactly what we were trying to
23 avoid by making that reservation on the list.

24 MR. FLATTMANN: Your Honor, we asked them to
25 revise their 282 list because it was a moving target. We

1 made that request in this courtroom, and the Court ordered
2 them to reduce their list by a date certain, and that is
3 what they did.

4 THE COURT: You can have a seat, Mr. Steuer.

5 And did they make the representation that
6 Mr. Steuer has represented they made in terms of a
7 reservation of rights?

8 MR. FLATTMANN: They attempted to reserve their
9 rights to present it as state of the art only, and that is
10 clearly what they're not doing.

11 THE COURT: I've heard enough, Mr. Flattmann.

12 MR. FLATTMANN: I'm sorry, your Honor?

13 THE COURT: I've heard enough.

14 MR. FLATTMANN: Thank you.

15 THE COURT: I'm going to overrule the objection.
16 I will not be invalidating the Ashley patents on the basis
17 of any reference including these eight that were not on the
18 revised 282, but I can see room for such references to be
19 cited as state of the art and perhaps corroborating evidence
20 to bolster what the expert is going to testify to. And when
21 we weigh in accordance with everything else that is
22 presented to us, we'll give it what weight it deserves. So
23 that objection is overruled.

24 What else from the plaintiff?

25 MS. RUPERT: Good morning, your Honor.

1 We have a couple of in limine objections with
2 respect to exhibits to be used in connection with the direct
3 of Dr. Stafford. The first is DTX-2217. That is the
4 declaration of Carrie Hontz. We have objected to the
5 admissibility of that on hearsay grounds. I had a meet and
6 confer with Mr. Reed shortly before court started, and I
7 understand Mylan is not seeking to admit that declaration so
8 that issue may be resolved.

9 THE COURT: He has not risen.

10 MS. RUPERT: We'll take that as a good thing.

11 MR. REED: I thought we had resolved that. We
12 won't seek to admit the declaration. That is merely a
13 custodian of records declaration.

14 THE COURT: Okay. They're not seeking to admit
15 it. Does that take care of that objection?

16 MS. RUPERT: That takes care of that objection.

17 My next objection relates to DTX-1842 and
18 DTX-2211. Right now, we are maintaining our hearsay
19 objections. Those exhibits are dated from IMS. It's
20 prescription data from a third-party sales and prescription
21 information company. Right now, we're attempting to reach
22 some sort of resolution with Mylan regarding admissibility
23 of this type of data. Mylan uses IMS data. Our clients
24 uses Wolters Kluwer. It's the same general type of data.

25 I provided the PTX numbers that we would like

1 Mylan to stipulate to the admissible to. Those are 542 and
2 565. From what I understand, Mylan has taken those under
3 advisement but we have not yet received a response from them
4 yet.

5 THE COURT: I've give them a chance after you
6 are done. Is there anything else on Dr. Stafford?

7 MS. RUPERT: Just one more thing.

8 On the demonstrative for Dr. Stafford, a number
9 of issues seem to be outside the scope of his report but I
10 will make those objections as they rise in the course of his
11 testimony.

12 THE COURT: Okay. Fine. That's it on
13 Dr. Stafford?

14 MS. RUPERT: That's it for Dr. Stafford.

15 THE COURT: Let's hear from Mr. Reed.

16 MR. REED: So the two DTX numbers, 1842 and
17 2211, that you referred to are documents that we will seek
18 the admission of. The declaration from the custodian of
19 records is what authenticates and obviates the hearsay rule
20 with respect to these two exhibits.

21 Just this morning, she gave me these PTX
22 numbers, and I said I would take a look at those, but I
23 don't think that we will be willing to agree to simply admit
24 all of the above. And so we will seek to admit 1842 and
25 2211.

1 THE COURT: When do you expect we'll get to
2 Dr. Stafford?

3 MR. REED: He will be as soon as we finish the
4 video testimony of Dr. Feldman, which will be 10 or
5 15 minutes once we start.

6 THE COURT: Okay. Then I guess we need to
7 resolve it now. Let's put aside PTX-542 and 565. Tell me
8 why your DTX-1842 and 2211 should be admissible and are not
9 hearsay. It's just based on the declaration?

10 MR. REED: The declaration establishes that the
11 data is maintained in the ordinary course of business by the
12 providers. It's a service that does this as part of their
13 business. It establishes how it was collected and who
14 collected it, when it was collected. It was provided as
15 part of this. That is what the declaration that was the
16 exhibit DTX-2217 establishes.

17 I believe that through the testimony of
18 Dr. Stafford we'll hear an explanation of how he obtained
19 that data, and then what he did with it, and that it will be
20 admissible.

21 THE COURT: Okay. Anything further from you on
22 Dr. Stafford?

23 MR. REED: I don't think so.

24 THE COURT: Okay. Any response?

25 MS. RUPERT: Yes, I would like to add that the

1 declaration now we're relying on to resolve the hearsay
2 issue is actually hearsay on hearsay, so I don't think that
3 would lead to the admissibility of evidence. DTX-18422 and
4 DTX-2211.

5 THE COURT: I'm going to overrule that
6 objection. I'm going to let Dr. Stafford testify as to
7 how he or she got this IMS data, and assuming he or she
8 testifies it is something that he or she relied on in
9 forming their expert report we'll go on to in a minute.

10 Any other objections from plaintiffs?

11 You have a full team today; right?

12 MR. FLATTMANN: A lot of witnesses today, your
13 Honor issue.

14 MS. WILGOOS: We also have objections to some of
15 the exhibits cited in Dr. Robbins' testimony and Dr. Robbins
16 is their expert concerning the Amin patents. Many of those
17 are similar to what Mr. Flattmann just argued with respect
18 to the 282 notice.

19 I certainly won't waste your Honor's time
20 rearguing that, but if I could just list the references for
21 you that we object to so that that is on the record, that
22 those should not be used as prior art in any way to
23 invalidate the patents. There is 15 of them.

24 It's DTX-1431, DTX-1442, DTX-1527, DTX-1597,
25 DTX-1605, DTX-1620, DTX-1627, DTX-1673, DTX-1765, DTX-1849,

1 DTX-1872, DTX-1879, DTX-2012, DTX-2074 and DTX-2079.

2 There are also several objections to documents
3 that were beyond the scope of Dr. Robbins' report. Mr. Reed
4 has represented that he won't play those so I consider that
5 resolved. If they come up, I will object during the
6 testimony.

7 And there is one other issue regarding two of
8 the demonstratives that they intend to use during
9 Dr. Robbins' testimony. The demonstratives are titled,
10 Plaintiffs' Experts Citations, and on these articles are
11 seven references that were never cited by plaintiffs'
12 experts. And so we believe that is improper, incorrect and
13 misleading. And those references, by the way, your Honor,
14 are the 15 references -- some of the 15 references that were
15 not cited in their 282 notice.

16 THE COURT: Okay. Thank you. Let's hear from
17 Mylan, please, with respect to Dr. Robbins.

18 MR. REED: Thank you, your Honor. I'm quite
19 surprised actually. I didn't understand their objection
20 until just this morning, and I'm not sure how to respond
21 without showing you what we're talking about.

22 THE COURT: Are you talking about
23 demonstratives?

24 MR. REED: I used the Elmo to show the actual
25 demonstrative.

1 THE COURT: That's okay. I'm going to overrule
2 that objection. If it's misleading or false you, can go
3 into it on cross-examination as a demonstrative. It's not
4 evidence, it's a bench trial, so I'm not going to worry
5 about that at the moment.

6 Did you want to address the others?

7 MR. REED: I think all the others, we had either
8 resolved or we have the same position as we did with respect
9 to Dr. Gilchrest.

10 THE COURT: Fine. My ruling on the 282 is the
11 same as it was with respect to the first witness. And if
12 it's beyond the scope of expert testimony, you can make the
13 objection on the record as we did yesterday.

14 Is there anything else from the plaintiffs this
15 morning?

16 MS. WILGOOS: No, your Honor.

17 THE COURT: Any issues the defendants wish to
18 raise?

19 MR. STEUER: No, your Honor.

20 THE COURT: Okay. One issue I had that we
21 talked about at the pretrial conference was post-trial
22 briefing, you all are going to agree on a date for your
23 opening brief, and we were going to try and come up with
24 some limitation on your proposed findings of fact. Have you
25 all met and conferred on those issues?

1 MR. REED: We have. With your agreement, we
2 propose that the parties submit opening post-trial briefs
3 simultaneously on July 21st not to exceed 30 pages. At the
4 same time, the parties would provide proposed findings of
5 fact and conclusions of law, not to exceed 50 pages.

6 THE COURT: A total of 50 for the findings of
7 fact and conclusion of law plus another 30 on the brief;
8 correct?

9 MR. REED: Yes.

10 THE COURT: So we would expect up to 80 pages
11 from each side on July 21st.

12 MR. REED: That's right.

13 THE COURT: Then you would finish your briefing
14 on July 29th.

15 MR. REED: Simultaneously file responsive briefs
16 not to exceed 20 pages on July 29th.

17 THE COURT: Okay. And that is agreed to by the
18 plaintiffs?

19 MS. WILGOOS: Yes, your Honor.

20 THE COURT: That's fine by us, and we will so
21 order that.

22 With that, I think we're up to the rest of the
23 Feldman deposition, correct?

24 MR. REED: Yes, your Honor. We recall
25 Dr. Lawrence Feldman via deposition. Yesterday, we left off

Feldman - designations

1 on or around page 67 of the deposition transcript; and with
2 the Court's permission, we'll start on page 67, line 22.

3 THE COURT: That's fine. Mr. Looby, could you
4 put some of the lights down, please.

5 (Feldman designations played as follows.)

6 "Question: Now, I think you testified before
7 that as of -- I can't recall if it was '99 or 2000 -- that
8 it was not believed that rosacea had a -- that bacteria were
9 involved in rosacea; is that correct?

10 "Answer: Correct.

11 "Question: During that time frame, wasn't it
12 thought that h pylori could be an organism involved in the
13 disease?

14 "Answer: It was a hypothesis but it had never
15 been proven.

16 "Question: Either true or false; correct?

17 "Answer: Correct.

18 "Question: But it was a theory that many people
19 believed?

20 "Answer: I wouldn't say many people. I think
21 that would be not true.

22 "Question: And is this the only portion of the
23 patient's record that you have from this visit ?

24 "Answer: Yes.

25 "Question: Do you know if the patient was on

Feldman - designations

1 any medications at the time of this visit?

2 "Answer: No.

3 "Question: Was this -- sorry. I may have asked
4 this, but was this the first visit you ever had with this
5 patient?

6 "Answer: No.

7 "Question: Was she a prior patient?

8 "Answer: She was a prior patient.

9 "Question: Is this the first time you diagnosed
10 her with rosacea?

11 "Answer: Yes.

12 "Question: Prior to this visit, did you see any
13 signs or symptoms of rosacea in this patient?

14 "Answer: No.

15 "Question: And subsequently in visits, you
16 never saw any signs or symptoms of rosacea either; correct?

17 "Answer: No. That's correct.

18 "Question: I think under the associated signs
19 and symptoms -- I'm sorry -- you said that had what?

20 "Answer: New pimples.

21 "Question: New pimples.

22 "Is that something that the patient reported to
23 you or that you observed subsequent to her last visit?

24 "Answer: That is what the patient reported.

25 "Question: Now, anywhere in this chart, did you

Feldman - designations

1 annotate a lesion count, a number of pimples that she had on
2 her face?

3 "Answer: I did not.

4 "Question: Other than the severity annotated as
5 moderate, did you put any numerical scale or any other type
6 of scale on the number of lesions that the patient had?

7 "Answer: No.

8 "Question: When you prescribed Periostat to
9 this patient, did you expect that it would reduce the
10 redness of rosacea?

11 "Answer: Yes.

12 "Question: And did you expect that it would
13 reduce the number of broken blood vessels?

14 "Answer: No.

15 "Question: Why not?

16 "Answer: Once the vessels are broken, the only
17 way to fix that is with a physical modality.

18 "Question: Such as laser therapy or something
19 like that?

20 "Answer: Yes.

21 "Question: Did you expect that Periostat would
22 avoid additional broken vessels?

23 "Answer: Yes.

24 "Question: Now, as I understand it, there was
25 no specific followup visit ever until today, where you

Feldman - designations

1 discussed the patient's rosacea with her again; is that
2 correct?

3 "Answer: Yes.

4 "Question: So you don't know, for example, if
5 she filled her Periostat prescription?

6 "Answer: Correct.

7 "Question: Correct, you don't know?

8 "Answer: I do not.

9 "Question: Okay. And you don't know whether
10 she took the rosacea -- the Periostat; correct?

11 "Answer: Correct.

12 "Question: And you don't know whether she took
13 it twice a day as you prescribed it; correct?

14 "Answer: Correct.

15 "Question: You never witnessed her taking the
16 medication?

17 "Answer: I did not.

18 "Question: And you never asked her in your
19 followup visit in 2004 whether she had taken Periostat?

20 "Answer: Correct.

21 "Question: And in that 2004 visit, she did not
22 mention her rosacea to you?

23 "Answer: Correct.

24 "Question: And you did not ask her about her
25 rosacea?

Feldman - designations

1 "Answer: Correct.

2 "Question: Did you ask her whether the
3 Periostat helped her at all?

4 "Answer: I did not.

5 "Question: So you never had any discussions
6 with this patient subsequently to determine whether the
7 Periostat successfully treated her rosacea; correct?

8 "Answer: Correct.

9 "Question: And you never observed her in a
10 follow-up visit to determine whether Periostat treated her
11 rosacea; correct?

12 "Answer: Correct.

13 "Question: Did you expect the patient to return
14 to you for a follow-up visit?

15 "Answer: Yes.

16 "Question: Let me ask you -- I know that -- let
17 me ask it to you this way. Are you surprised that in the
18 ten years since you diagnosed rosacea, that you have not
19 seen this patient again for that treatment?

20 "Answer: I wouldn't say I was surprised. I
21 mean, that happens. People get busy or they -- maybe she
22 went to another dermatologist. Maybe she moved. You know,
23 there's lots of reasons why people don't come back.

24 "Question: Sure. Between 2000 and 2004, would
25 you expect that any patient would never have a subsequent

Feldman - designations

1 flare-up of rosacea from the first one?

2 "Answer: No. I would expect that she -- you
3 know, the normal course which she would have other flare-ups
4 during that period.

5 "Question: Is it possible that your diagnosis
6 of rosacea in this patient was a misdiagnosis given that you
7 never heard that complaint from her again, at least in the
8 four years?

9 "Answer: No. I'm sure that she had rosacea.
10 It's just a very, very clear-cut diagnosis that someone
11 with -- who has been a dermatologist for awhile, it would be
12 very hard to miss a diagnosis of rosacea.

13 "Question: And it couldn't be confused, for
14 example, with some other dermatitis or skin rash caused by
15 environmental factors once she changed her soap or something
16 like that?

17 "Answer: It would be hard to say that. I would
18 say that I don't think that's the case.

19 "Question: But it's possible?

20 "Answer: Again, I feel a hundred-percent
21 comfortable that she had rosacea in my diagnosis.

22 "Question: Now, you never determined
23 specifically on this patient whether the Periostat caused a
24 reduction in lesion count and the number of pimples that
25 this patient had?

Feldman - designations

1 "Answer: Yes. Yes, I did not. I did not
2 determine that.

3 "Question: Did you know for certain when you
4 prescribed Periostat whether it would reduce lesion count of
5 the patient?

6 "Answer: No.

7 "Question: Did you provide this patient with
8 any sample of Periostat?

9 "Answer: I did not.

10 "Question: Now, going back to this
11 February 19th chart, you mentioned that in this bottom
12 right-hand corner, I think you said it was a copy of the
13 prescription?

14 "Answer: It was -- my standard is to write down
15 what I had given as a prescription so that I would have a
16 record of what I had given her.

17 "Question: So I just want it to be clear. It's
18 not any type of photocopy?

19 "Answer: No.

20 "Question: Now, the actual prescription that
21 you filled out, does that give any indication of what --
22 why the medication was prescribed?

23 "Answer: It did not.

24 "Question: When you saw this patient, were you
25 conducting research concerning rosacea?

Feldman - designations

1 "Answer: No.

2 "Question: Were you planning to conduct any
3 research concerning rosacea?

4 "Answer: No.

5 "Question: Was there anyone else present with
6 you during the patient visit?

7 "Answer: No.

8 "Question: Was the patient taking any notes
9 during your visit?

10 "Answer: I don't know.

11 "Question: Not that you recall?

12 "Answer: Not that I recall. It's a long time
13 ago.

14 "Question: The February 19th record does not
15 indicate that you took any skin samples from this patient;
16 correct?

17 "Answer: Correct.

18 "Question: And at no time did you determine
19 whether there was a change in the patient's skin microflora
20 while the patient was taking Periostat; correct?

21 "Answer: Correct.

22 "Question: Are you a microbiologist?

23 "Answer: No.

24 "Question: Other than sort of your general
25 medical education, do you have any other education or

Feldman - designations

1 training in microbiology?

2 "Answer: No, I done do not.

3 "Question: And I apologize if I asked you this
4 before, but you never discussed the patient's -- you never
5 discussed with the patient whether or not she took the
6 Periostat; correct?

7 "Answer: Correct.

8 "Question: Prior to April of 2000, did you
9 prescribe Periostat to any other patient other than the one
10 listed in this patient record we have been discussing?

11 "Answer: I can't recall without seeing a
12 record.

13 "Question: After your conversation with
14 Mr. Delafield, did you search for other patient records
15 prior to April of 2000 in which you may have prescribed
16 Periostat?

17 "Answer: Yes.

18 "Question: And you weren't able to find any?

19 "Answer: No.

20 "Question: Did you publish in any way your
21 treatment of this patient with Periostat?

22 "Answer: No.

23 "Question: Did you consider doing so?

24 "Answer: No.

25 "Question: You never submitted, for example, a

Feldman - designations

1 case study to a journal or a magazine?

2 "Answer: No.

3 "Question: Did you ever present a case study of
4 this patient at a conference?

5 "Answer: No.

6 "Question: Did you ever disclose at a
7 conference that you ever prescribed Periostat to this
8 patient?

9 "Answer: No.

10 "Question: Did you ever make your treatment of
11 this patient with Periostat public in any other way?

12 "Answer: No.

13 "Question: Did you ever attempt to sell the
14 idea of using Periostat to treat rosacea?

15 "Answer: No.

16 "Question: Did you ever call up CollaGenex and
17 say, hey, you can use Periostat to treat rosacea?

18 "Answer: No.

19 "Question: Did you ever consider submitting a
20 patent application for the use of Periostat to treat
21 rosacea?

22 "Answer: No.

23 "Question: I said why didn't you do any of
24 those things?

25 "Answer: It's not what I do. I am just a

Feldman - designations

1 regular dermatologist and take care of patients.

2 "Question: Apart from the specific
3 prescription, have you ever written anything about the use
4 of Periostat in the treatment of rosacea?

5 "Answer: No.

6 "Question: Was there anything about this
7 February 19, 2000 patient specifically that led you to
8 prescribe Periostat for her?

9 "Answer: No.

10 "Question: Did you use any systematic method
11 with any of your patients in which you prescribed Periostat
12 to determine whether Periostat was effective to treat their
13 rosacea?

14 "Answer: Just visual examination. Just my
15 routine.

16 "Question: But, for example, you didn't do
17 lesion counts for any of the patients --

18 "Answer: Correct. I did not.

19 "Question: -- you prescribe Periostat for.

20 "Did you take any notes at this conference?

21 "Answer: I might have, but I didn't keep them.

22 "Question: So you don't have any current notes
23 currently that you took of that conference?

24 "Answer: No.

25 "Question: Do you have any abstracts of the

Feldman - designations

1 conference?

2 "Answer: No.

3 "Question: That were handed out at the
4 conference?

5 "Answer: (Witness shakes head no.)

6 "Question: Do you have any symposia?

7 "Answer: No.

8 "Question: Anything written at all from this
9 conference?

10 "Answer: No, I do not.

11 "Question: No -- you don't have, for example,
12 any list of the speakers or an agenda for the meeting?

13 "Answer: No.

14 "Question: Now, you mentioned that the speaker
15 had experience with Periostat, but you were not sure if that
16 was personal experience or not. So -- is that correct?

17 "Answer: Yes.

18 "Question: So did you understand listening to
19 this that this was an anecdotal report?

20 "Answer: Yes.

21 "Question: And so there wasn't any specific
22 clinical evidence that you were aware of that Periostat
23 worked for the signs and symptoms -- to treat the signs and
24 symptoms of rosacea?

25 "Answer: Correct.

Feldman - designations

1 "Question: Prior to February -- prior to
2 February 19, 2000, were you personally aware of anyone who
3 had prescribed Periostat for the treatment of rosacea?

4 "Answer: No.

5 "Question: At that conference, do you recall
6 any specific mention of whether Periostat was effective to
7 treat the papules or pustules of rosacea?

8 "Answer: It was a very long time ago. I just
9 remember the general idea that this was sort of a new kind
10 of idea in dermatology where an antibiotic could work as an
11 anti-inflammatory and not to kill bacteria and it was just
12 the dawn of that whole idea.

13 "Question: When you said it was a new idea, it
14 was your understanding that it had not been tested
15 clinically at that time; correct?

16 "Answer: Correct. And I don't know if it had
17 been tested clinically at that time.

18 "Question: But the speaker at the conference to
19 your recollection did not report that it had been
20 successfully clinically tested at that time; correct?

21 "Answer: Correct.

22 "Question: Did you ever read the package insert
23 prior to prescribing Periostat in February of 2000?

24 "Answer: No.

25 "Question: Do you have a duty of

Feldman - designations

1 confidentiality to your patients?

2 "Answer: Yes.

3 "Question: And what does that duty consist of?

4 Can you just describe it for me generally?

5 "Answer: If they tell me something, I'm not
6 going to tell somebody else about it.

7 "Question: Okay.

8 "Answer: You know, like if you told me that you
9 ate red raspberries, I can't tell anybody else that you did
10 that.

11 "Question: Even something as simple as that?

12 "Answer: Right.

13 "Question: And do you consider this an ethical
14 responsibility?

15 "Answer: Yes.

16 "Question: It's also a legal responsibility;
17 correct?

18 "Answer: Yes.

19 "Question: A legal duty?

20 "Answer: Yes.

21 "Question: Do you discuss treatment of your
22 patients with anyone?

23 "Answer: Yes. I mean, sometimes -- not always,
24 but sometimes I will discuss them with other physicians.

25 "Question: Do you consider that consistent with

Feldman - designations

1 your duty of confidentiality to discuss it with other
2 physicians?

3 "Answer: Yes. I think according to HIPAA, you
4 are allowed to ask about -- as long as you don't identify
5 the patient and there's no way that the doctor would know
6 who you are talking about.

7 "Question: And in the instances where you do
8 that, has it been for the patient's benefit and treatment?

9 "Answer: Yes.

10 "Question: Apart from this litigation, have you
11 ever disclosed the February 19th patient chart, February 19,
12 2000 patient chart to anyone else?

13 "Answer: No.

14 "Question: This storage facility that you
15 mentioned, is that a secure facility?

16 "Answer: Yes. It's locked.

17 "Question: And so only you or someone on your
18 staff would have access to it; correct?

19 "Answer: That's correct.

20 "Question: Did you obtain any authorization
21 from the patient to disclose their chart in the context
22 letter of this litigation?

23 "Answer: No.

24 "Question: And it's your opinion that you
25 didn't have to do that pursuant to HIPAA?

Feldman - designations

1 "Answer: Right. When Mr. Delafield asked me to
2 get it, I asked him if I had to get any kind of
3 authorization. He said I didn't because I wasn't
4 transmitting anything where anybody would know who this
5 patient is. There's no way to know who this patient is.

6 "Question: To your knowledge, is Periostat --
7 does Periostat act as an antibiotic?

8 "Answer: No.

9 "Question: Does Oracea act as an antibiotic?

10 "Answer: No.

11 "Question: Did Mr. Shulman or Mr. Delafield in
12 that meeting yesterday discuss with you specific questions
13 that they intended to ask you?

14 "Answer: Yes.

15 "Question: And did you do a rehearsal of the
16 questions and answers that you would give during the
17 deposition?

18 "Answer: Yes.

19 "Question: And did they advise you specifically
20 how to answer or not to answer certain questions?

21 "Answer: No. Well, I mean the only advice they
22 gave was to tell the truth and just, you know, just tell the
23 whole truth.

24 "Question: Did they suggest ways for you to
25 answer the questions?

Feldman - designations

1 "Answer: No, I don't think so.

2 "Question: For example, did they say, you know,
3 make sure you mention that you used Periostat regardless of
4 whether the question is asked or not?

5 "Answer: No. No. They definitely didn't do
6 that.

7 "Question: Did they advise you of questions
8 that Galderma's lawyers were likely to answer?

9 "Answer: No. They didn't.

10 "Question: To ask you. I'm sorry.

11 "Answer: No.

12 "Question: Did you -- did they do a mock
13 cross-examination of you?

14 "Answer: No.

15 "Question: Pretending they were Galderma's
16 lawyers?

17 "Answer: No.

18 "Question: Did they give you any written list
19 of the questions that they would ask you?

20 "Answer: No.

21 "Question: Do you personally take rosacea for
22 your -- sorry. Do you personally take Oracea to treat your
23 rosacea?

24 "Answer: Yes. It's right in my cabinet over
25 here.

Feldman - designations

1 "Question: Do you think it successfully treats
2 your rosacea?

3 "Answer: Yes.

4 "Question: Do you know of what a bisphosphonate
5 compound is?

6 "Answer: I do not.

7 "Question: Did you prescribe a bisphosphonate
8 compound to be taken by the patient of Exhibit A at the time
9 that you prescribed the Periostat?

10 "Answer: I did not.

11 "Question: In the January, February, March 2000
12 time frame, was there anything that prevented you from
13 telling other doctors that a form of treatment that you were
14 using to treat rosacea was to prescribe Periostat twice
15 daily?

16 "Answer: No.

17 "Question: Was there anything which prevented
18 the patient of Exhibit A from telling whomever she felt like
19 telling that she was diagnosed with rosacea and being
20 treated for it with Periostat twice a day?

21 "Answer: No.

22 "Question: You evidence earlier that you had --
23 you were suffering from rosacea at the time you were taking
24 the Periostat in late '99 and early 2000. Do you recall
25 that?

Feldman - designations

1 "Answer: Yes.

2 "Question: And I believe you said that you
3 noticed that your rosacea condition improved after taking
4 the Periostat?

5 "Answer: Yes.

6 "Question: How did it improve? What did you
7 notice?

8 "Answer: I noticed that I was getting less
9 pimples. I tend to get like these little tiny pimples
10 especially on my chin area, and I noticed I was getting less
11 of those and less red. And I also just -- it sounds funny,
12 but one of the patients actually mentioned that my face
13 looked better. He noticed it. What are you doing? I
14 remember him saying, you know, your skin looks better.

15 "Question: Now, when you ordered the subsequent
16 supply -- order is the wrong term. When you got the
17 professional courtesy samples from --

18 "Answer: CollaGenex.

19 "Question: CollaGenex in late January or early
20 February of 2000 of the Periostat, were you obtaining those
21 samples to treat your gingivitis condition, your rosacea
22 condition, or both or neither?

23 "Answer: I would say at that time, both. I
24 mean, you know, I had started doing it to treat my
25 gingivitis because the periodontist told me to, but then

Feldman - designations

1 once it was helping for the rosacea, I wanted to do it for
2 both.

3 "Question: Let me ask you this way. Did you
4 disclose to any other dermatologists that you had used
5 Periostat to treat rosacea?

6 "Answer: No.

7 "Question: Did you discuss with any other
8 dermatologists your own personal use of Periostat and the
9 results it had on your rosacea?

10 "Answer: No.

11 "Question: Are you aware of the patient in the
12 February 19, 2000 chart discussing with anyone else whether
13 or not she used Periostat to treat rosacea?

14 "Answer: No.

15 "Question: Prior to your own use of Periostat,
16 did you perform a lesion count of the pimples that you had
17 related to rosacea?

18 "Answer: On me?

19 "Question: Yes.

20 "Answer: No.

21 "Question: And did you do that subsequent to
22 your treatment with Periostat?

23 "Answer: No.

24 "Question: And once you finished the course,
25 your course of -- your initial course of treatment with

Feldman - designations

1 Periostat, I think you testified, and I just want to verify
2 that your periodontist advised you to continue taking
3 Periostat to treat your gum disease; correct?

4 "Answer: Yes.

5 "Question: Okay. With respect to the patient
6 in the February 19, 2002 chart, was it important to you one
7 way or the other whether she was taking a bisphosphonate
8 drug at the time?

9 "Answer: I would say no, because I wasn't aware
10 of any drug interactions with that.

11 "Question: Okay. So you would have prescribed
12 Periostat regardless of whether or not she was taking a
13 bisphosphonate drug?

14 "Answer: Yes.

15 (Deposition designation concludes.)

16 THE COURT: That concludes the deposition. You
17 can call your next witness.

18 MS. WESTIN: Mylan calls Dr. Randall Stafford.

19 THE COURT: Okay.

20 ... RANDALL SCOTT STAFFORD, having been placed
21 under oath at 9:12 a.m. as a witness, was
22 examined and testified as follows

23 THE COURT: Good morning, Dr. Stafford.

24 THE WITNESS: Good morning.

25 THE COURT: Counsel, remind us who you are.

Stafford - direct

1 Then you may proceed.

2 MS. WESTIN: Your Honor, my name is Lori Westin
3 from Mylan.

4 THE COURT: You may proceed.

5 MS. WESTIN: Thank you, your Honor.

6 DIRECT EXAMINATION

7 BY MS. WESTIN:

8 Q. Good morning, Dr. Stafford. Would you please
9 introduce yourself to the Court?

10 A. Good morning. My name is Randall Scott Stafford.

11 Q. Dr. Stafford, did you prepare a slide presentation to
12 assist you today?

13 A. Yes, I did.

14 Q. How did you prepare them?

15 A. I prepared slides for this testimony with the
16 assistance of counsel.

17 MS. WESTIN: Can we bring up DDX-101? 102. I'm
18 sorry.

19 BY MS. WESTIN:

20 Q. Dr. Stafford, can you briefly describe your
21 educational background?

22 A. I obtained a bachelor degree in sociology from Reed
23 College in 1980.

24 I have two master's degrees, the first from
25 Johns Hopkins in 1982 in Health Administration and Planning

Stafford - direct

1 okay, the second from UC Berkeley in 1988 in Health and
2 Medical Sciences.

3 I also completed my Ph.D. work in epidemiology
4 at UC Berkeley in 1990 and graduated from UC San Francisco
5 with my medical degree in 1992.

6 Q. Did you complete any training after receiving your
7 doctorate degree?

8 A. Yes, I did. I completed a post-doctoral fellowship
9 with the Center for Disease Control in 1991. I also
10 completed my clinical training in internal medicine at
11 Massachusetts General Hospital in 1994.

12 Q. And what is your current position?

13 A. I'm an Associate Professor of Medicine at Stanford
14 University.

15 Q. Do you hold other positions at Stanford?

16 A. Yes, I do. I am the Program Director of the
17 Prevention Research Center's Program on Prevention Outcomes
18 and Practices. I am also the Codirector of the Research
19 Center's Training Program For Post-Doctoral Fellows and
20 Medical Students.

21 Q. Do you hold any clinical appointments?

22 A. Yes. I'm on staff at the Stanford hospital and
23 clinics as well as the Stanford Medical Center. I generally
24 see patients at least once per week.

25 Q. Do you have any scientific publications in clinical

Stafford - direct

1 epidemiology?

2 A. I have authored or coauthored over 200 references
3 including research articles, abstracts, reviews, book
4 chapters, government reports.

5 Q. And are you a reviewer for scientific journals?

6 A. I regularly review peer reviews, including the New
7 England journal of Medicine, the American Medical
8 Association, Archives of Internal Medicine and the American
9 Journal of Preventive Medicine.

10 I am currently on the Board of Directors of the
11 American Journal of Preventive Medicine. I also serve on
12 the Editorial Board of Primary Prevention Insights. This is
13 a peer-reviewed journal that focuses on clinical
14 epidemiology issues.

15 Q. Dr. Stafford, could you please tell us about your
16 research in the clinical epidemiology field?

17 A. For the last 25 years, my research is focused on
18 documenting and evaluating physician practice patterns. By
19 this, I mean using national level data such as available
20 from IMS to examine the decisions that physicians make in
21 their practices and the subsequent effect of those decisions
22 on patient outcomes. I have looked at multiple types of
23 physician practice but largely have focused on physician
24 prescribing.

25 Off-label prescribing is among my interests and

Stafford - direct

1 I have published a number of papers on this topic.

2 Q. Dr. Stafford, what is IMS Health?

3 A. IMS Health is a private research market company.

4 They collect and develop data on pharmaceutical prescribing,
5 both United States and elsewhere. In general, their data is
6 often used by the pharmaceutical industry both for their
7 strategic purposes as well as operational purposes.

8 Q. Do you use IMS Health provided data in your research?

9 A. Yes. IMS Health has been kind enough to provide me
10 with information that I use in my research. In fact,
11 database information from IMS Health is critical to my
12 research.

13 Q. And which IMS Health products do you work with?

14 A. I have used a number of different products, among
15 them the National Disease and Therapeutic Index or NDTI.
16 This is a physician survey conducted nationally.

17 I also make use of the National Prescription
18 Audit or NPA, and the Xponent database. These are both
19 derived from the IMS Health Next Generation Prescription
20 Service.

21 Q. You also list on your slide a position as a member of
22 an advisory group to IMS Health. What is this position?

23 A. For the last three years I've been a member of an
24 advisory group that provides advice to IMS Health on their
25 collaborations with academic researchers.

Stafford - direct

1 Q. Do you consider yourself an expert in analyzing and
2 reviewing IMS Health data?

3 A. Yes. For the last 13 years, I've had extensive
4 experience analyzing and applying data from IMS Health.

5 MS. WESTIN: Your Honor, may I approach the
6 bench with demonstratives and exhibits?

7 THE COURT: You may.

8 (Documents passed forward.)

9 BY MS. WESTIN:

10 Q. Dr. Stafford, did you prepare a CV of your relevant
11 experience?

12 A. Yes, I did.

13 Q. Is this defendants' document DTX-2208 in your binder?

14 A. Yes, it is.

15 MS. WESTIN: Your Honor, we offer DTX-2208.

16 THE COURT: Any objection?

17 MS. RUPERT: No objection.

18 THE COURT: It's admitted.

19 (DTX-2208 received into evidence.)

20 MS. WESTIN: Your Honor, at this time we would
21 like to offer Dr. Stafford as an expert in clinical
22 epidemiology, including the use of national databases of US
23 prescription patterns such as those generated by IMS Health.

24 MS. RUPERT: No objection.

25 THE COURT: He is so recognized.

Stafford - direct

1 MS. WESTIN: Can I get DDX-103, please.

2 BY MS. WESTIN:

3 Q. Dr. Stafford, what you have been asked to do in
4 connection with this trial?

5 A. I have been asked to review and assess prescription
6 data on Periostat between 1998 and the year 2002 that was
7 obtained by Mylan from IMS Health.

8 Q. Dr. Stafford, is this a summary that you prepared of
9 your opinions that you will offer in this case?

10 A. Yes, it is.

11 Q. And what opinions will you be offering today?

12 A. Well, in summary, based both on the Periostat data
13 available from IMS Health as well as the off-label
14 prescribing practices of dermatologists, it is my opinion
15 that dermatologists were prescribing Periostat prior to
16 April 2002 for dermatologic conditions, including rosacea.

17 Also based on the Periostat data, it is my
18 opinion that at least one Periostat prescription was written
19 by Dr. Feldman and filled in March 2000.

20 Finally, the Periostat prescription written by
21 Dr. Feldman and filled in March 2000 is likely the same
22 prescription represented in Dr. Feldman's patient record.

23 MS. WESTIN: Can we get DDX-104, please.

24 BY MS. WESTIN:

25 Q. What materials or information did you consider in

Stafford - direct

1 forming your opinions?

2 A. I relied on a number of materials, including the
3 Periostat prescription data from IMS Health, the
4 prescription record and the declaration provided by
5 Dr. Feldman, Dr. Feldman's testimony, the declaration of
6 Karrie Hontz of IMS Health, the scientific literature,
7 plaintiffs' expert witness and, of course, my own education,
8 experience and knowledge.

9 Q. Thank you, Dr. Stafford. Can you tell us what is
10 Periostat?

11 A. Periostat is a 20 milligram doxycycline formulation.

12 Q. And in early 2000, what indication was Periostat
13 approved for by the FDA?

14 A. The FDA had approved Periostat for use in
15 periodontitis, as an treatment of periodontitis.
16 Periodontitis is a periodontal disease.

17 Q. Was Periostat approved for any other indication?

18 A. No. Periostat has only been approved for use as an
19 adjunct treatment of periodontitis. That was true in early
20 2000. That remains true today.

21 Q. Dr. Stafford, with regards to your opinions that you
22 will offer today, what information did you rely on from IMS
23 Health?

24 A. I used IMS Health information available from their
25 Next Generation Prescription Service, NGPS, which includes

Stafford - direct

1 information from the Xponent database as well as the
2 National Prescription Audit.

3 Q. And what is the NGPS database?

4 A. NGPS is a family of databases that use information
5 obtained during pharmacy transactions.

6 MS. WESTIN: Can I get DDX-105, please.

7 BY MS. WESTIN:

8 Q. Is this represented in your next slide?

9 A. Yes, it is.

10 Q. And can you explain your diagrams?

11 A. As you can see here, when a prescription is filled at
12 either a mail order or retail pharmacy, information is
13 collected by the pharmacy. IMS Health obtains that data and
14 uses that information to make projections about prescribing
15 practices. That data generates databases at a regional
16 level or down to the physician level in the Xponent
17 database. National estimates are available in the national
18 prescription audit.

19 Q. And what type of information is recorded in the NGPS
20 database?

21 A. NGPS includes information on both the prescription as
22 well as the prescriber. Details about the prescription
23 include things like the drug name, the dose of the drug, the
24 patient instructions, for instance, how frequently to take
25 it, what route of administration, also the number of units

Stafford - direct

1 dispensed and the number of refills.

2 Q. And how is the prescriber information recorded by IMS
3 Health?

4 A. IMS Health has a unique position identifier that is
5 often obtained via the physician's drug enforcement agency
6 or DEA number or increasingly the national physician
7 identifier. Information on this physician is obtained from
8 other sources, for instance, from the American Medical
9 Association master file which records the physician's
10 specialty.

11 Q. Dr. Stafford, can you please turn to DTX-1842 which
12 is that large second binder.

13 Is this the Periostat prescription data provided
14 by IMS Health that you reviewed in this case?

15 A. Yes, it is.

16 Q. And what is this document?

17 A. This is a spreadsheet listing of individual health
18 professionals, both medical professionals as well as dental
19 professionals. It includes information on both new and
20 refill Periostat prescriptions that occurred between 1998
21 and the year 2000.

22 MS. WESTIN: Your Honor, I offer DTX-1842.

23 MS. RUPERT: Your Honor, our objection to the
24 admissibility of this exhibit are on record as of this
25 morning.

Stafford - direct

1 THE COURT: They have been overruled already so
2 the document is admitted.

3 MS. WESTIN: Thank you, your Honor.

4 (DTX-1842 received into evidence.)

5 BY MS. WESTIN:

6 Q. Dr. Stafford, is there an extract of the data that
7 you provided today?

8 A. Yes. As you can see, this is a rather large
9 document. What I have done is prepare several pages which
10 include information on Dr. Feldman.

11 Q. And is this document DTX-2211 in your binder?

12 A. Yes, it is.

13 Q. And have you reviewed this document?

14 A. Yes, I have.

15 MS. WESTIN: Your Honor, I offer DTX-2211.

16 MS. RUPERT: Your Honor, our objections to the
17 admissibility of this exhibit are also on record as of this
18 morning.

19 THE COURT: They have been overruled, and the
20 document is admitted.

21 (DTX-2211 received into evidence.)

22 BY MS. WESTIN:

23 Q. Dr. Stafford, the "Dr. Feldman" that you just
24 referred to, is that the same Dr. Feldman that testified
25 here today?

Stafford - direct

1 A. Yes, it is.

2 Q. And how do you know that this Dr. Feldman is the
3 Dr. Feldman that is referred to in DTX-2211?

4 A. It's in the IMS Health Periostat data. Dr. Feldman
5 is listed on line 5311.

6 Q. And did you compare this data to anything else?

7 A. The address listed for Dr. Feldman is the same as he
8 provided in his deposition.

9 Q. What information is presented in DTX-2211?

10 A. This includes information on the individual physician
11 along with their specialty. It includes information on the
12 number of projected new and total prescriptions that were
13 dispensed at a pharmacy providing information to IMS
14 Health --

15 Q. And what do you mean -- I apologize. Did you finish
16 your answer?

17 A. By pharmacies for that time period.

18 Q. What do you mean by projected prescriptions?

19 A. IMS Health, in its process of developing these data,
20 needs to make up or compensate for data from pharmacies that
21 are not recorded data. Therefore, they take the raw
22 information and provide projections based on statistical
23 element.

24 THE COURT: Did you have an objection?

25 MS. RUPERT: I do. Your Honor, I want to enter

Stafford - direct

1 for the record an objection to DDX-106 that they just put up
2 on the screen. This is outside the scope of Dr. Stafford's
3 report. In his report, he did not name a single physician
4 other than Dr. Feldman.

5 THE COURT: The objection is noted. We'll take
6 it under advisement post-trial.

7 You may continue with your examination.

8 MS. WESTIN: Thank you, your Honor.

9 BY MS. WESTIN:

10 Q. Dr. Stafford, is the information on this slide
11 derived from DTX-2211?

12 A. Yes, it is.

13 Q. Thank you. And why did you prepare this slide for
14 us?

15 A. I prepared this slide because even though 2211 is
16 much smaller, it's still very difficult to review. I
17 prepared this slide in order to make several points about
18 the data contained in this database. As you can see, this
19 is a listing of physicians. All of these physicians
20 prescribed Periostat prior to April of 2000. For instance,
21 on the first line, you see Dr. Michaela McDonnell, a
22 dermatologist from Colorado. If we dig a little deeper into
23 her data on the next slide, we can see that in the column M,
24 we have a listing for new prescriptions NRX that were
25 dispensed in September of 2000.

Stafford - direct

1 THE COURT: Hold on.

2 Do you have an objection?

3 MS. RUPERT: Again, I would like to object to
4 the use of this demonstrative, DDX-107, outside the scope of
5 Dr. Stafford's expert report. His expert report did not
6 name a single physician other than Dr. Feldman.

7 THE COURT: Are there any other slides that are
8 going to be used that you have the same objection for?

9 MS. RUPERT: Indeed. DDX-109.

10 I have other objections to subsequent
11 demonstratives but they will be on other grounds. They will
12 still be outside the scope.

13 THE COURT: Let's get on the record now all of
14 your objections that are based on outside the scope of the
15 expert report.

16 MS. RUPERT: Absolutely. Okay. I'll repeat
17 them all. DDX-106, DDX-107, DDX-109, and DDX-114.

18 THE COURT: You object to all of them as outside
19 the scope of the report.

20 MS. RUPERT: Absolutely.

21 THE COURT: Those are all noted.

22 You may continue.

23 BY MS. WESTIN:

24 Q. Dr. Stafford, the information on this slide, is it
25 derived from DDX-2211?

Stafford - direct

1 A. Yes, it is.

2 Q. Do you want to continue with your explanation of
3 column M?

4 A. As I said column M, we have a listing of new
5 prescriptions that were provided and dispensed in September
6 of 2000. The figure 1.14 represents the number of projected
7 prescriptions written by Dr. McDonnell in this month.

8 This projection compensates for those pharmacies
9 that are not covered by IMS Health. This is not a whole
10 integer number because IMS Health needs to apply a
11 statistical algorithm to increase the size of the number of
12 prescriptions to make up for those prescriptions that were
13 not reported by IMS Health.

14 Q. Is there ever a situation where a value is presented
15 but no prescription was written by a physician?

16 A. In every case, a nonzero projection is based on an
17 actual prescription that was written by a physician and
18 filled at a pharmacy.

19 Q. Before we go on, can you please explain what column
20 AW is?

21 A. In addition to listing new prescriptions, the data in
22 2211 also lists total prescriptions which are the sum of new
23 prescriptions and refill prescriptions.

24 As you can see in column AW, Dr. McDonnell has
25 listed 1.14 as her total prescriptions. Since this is the

Stafford - direct

1 same as the new prescriptions, this indicates that in that
2 month, she only had new prescriptions being dispensed by a
3 pharmacy.

4 MS. WESTIN: Can I get DDX-108, please.

5 BY MS. WESTIN:

6 Q. Dr. Stafford, what is your first opinion you will be
7 presenting today?

8 A. It's my opinion that dermatologists were prescribing
9 Periostat prior to April 6, 2000 for dermatologic
10 conditions, including rosacea.

11 MS. WESTIN: And next slide.

12 BY MS. WESTIN:

13 Q. Dr. Stafford, can you speak again as to the
14 dermatologists that were represented in the entire data set?

15 A. Yes. This is another extract which lists
16 dermatologists that were prescribing Periostat prior to
17 April of 2000. As you can see, among the 67 dermatologists
18 that were prescribing before April 2000, we have eight
19 examples here which are distributed widely across the United
20 States representing multiple regions of the country.

21 Q. And in this slide, did you derive this information
22 from DTX-2211, the large document?

23 "Answer: I derived these from DTX-1842.

24 "Question: Thank you for correcting me.

25 And what does this mean in regards to this

Stafford - direct

1 slide?

2 "Answer: The range and number of dermatologists
3 suggests that Periostat use prior to April 2000 among
4 dermatologists was widespread.

5 MS. RUPERT: Your Honor, I wanted to object to
6 the scope of the testimony as outside the scope of his
7 expert report.

8 THE COURT: The objection is noted.

9 BY MS. WESTIN:

10 Q. Were you surprised by this?

11 A. No. In fact, I wasn't. Dermatologists often
12 prescribe drugs off label. Periostat was not an exception.

13 Q. How common is off label use in dermatology?

14 A. Off label prescribing is very common in dermatology.
15 Dermatologists often face clinical situations where FDA-
16 approved therapies are not adequate for them to treat the
17 patients they see in practice.

18 Q. And what is your support for this conclusion?

19 A. I base this on my own clinical experience and my
20 research as well as the scientific literature, particularly
21 two papers, one by Li published in 1998, another by Sugarman
22 in 2002.

23 Q. Dr. Stafford, are DTX-2218 and DTX-2214 the Li and
24 Sugarman articles respectively?

25 A. Yes, they are.

Stafford - direct

1 Q. And have you reviewed the Li and Sugarman articles?

2 A. Yes.

3 MS. WESTIN: Your Honor, I offer DTX-2218 and
4 2214.

5 MS. RUPERT: No objection, your Honor.

6 THE COURT: They're admitted.

7 (DTX-2281 and DTX-2214 were admitted into
8 evidence.)

9 MS. WESTIN: Can I get the next slide?

10 BY MS. WESTIN:

11 Q. What does the Li reference disclose regarding the off
12 label prescribing practice of dermatologists?

13 A. This studies shows that among the 55 dermatologists
14 surveyed, all of them reported prescribing at least one drug
15 off label for dermatologic conditions.

16 Q. And what is the significance of this information?

17 A. This suggests that dermatologists frequently use
18 drugs off label in practice.

19 MS. WESTIN: Can we turn to the next slide,
20 please?

21 BY MS. WESTIN:

22 Q. And the Sugarman reference, what does it disclose?

23 A. It shows that rosacea was the skin condition most
24 likely to be treated with off label prescribing.

25 Q. And the table on this slide, what does it represent?

Stafford - direct

1 A. This is data from a federally collected survey of
2 physicians nationally. It indicates that for rosacea, 73
3 percent of treatment made use of off label prescribing.

4 Q. Did Sugarman identify off label drugs that were used
5 by dermatologists to treat rosacea?

6 A. They found that the tetracycline drugs, including
7 tetracycline itself, minocycline, and doxycycline, were the
8 most frequently prescribed drugs for rosacea. In fact, the
9 tetracycline drugs accounted for almost 50 percent of all
10 rosacea treatment.

11 Q. And how is this relevant to your opinion regarding
12 the Periostat prescription data from IMS Health?

13 A. This report reinforces my impression that
14 dermatologists frequently use off label prescribing in their
15 practices, including for the treatment of rosacea using
16 tetracycline drugs.

17 MS. WESTIN: Can we get the next slide, please?

18 BY MS. WESTIN:

19 Q. Dr. Stafford, can you please remind us what your next
20 opinion is?

21 A. It's my opinion that at least one Periostat
22 prescription was written by Dr. Feldman and filled March
23 2000.

24 Q. Dr. Stafford, what is the basis for you opinion?

25 A. I base this opinion again on the IMS Health Periostat

Stafford - direct

1 prescription data as well as the off label prescribing
2 practices of dermatologists.

3 Q. Do you rely on any other support for your opinion?

4 A. I also rely on information provided in a declaration
5 by Kerrie Hontz of IMS Health, who is a leader in this
6 field.

7 MS. WESTIN: Can I get the next slide, please?

8 BY MS. WESTIN:

9 Q. And what support was provided by Ms. Hontz?

10 A. Ms. Hontz confirmed my understanding that wherever a
11 projected prescription value is made, this projection is
12 made on an actual underlying prescription.

13 Q. Concentrating on the data provided for Dr. Feldman
14 specifically, what does this information disclose?

15 A. Again, this is an extract that I've made which
16 isolates the information on Dr. Feldman to make it more
17 apparent.

18 Q. Dr. Stafford, is this information -- I'm sorry for
19 interrupting. Is this information provided in DTX-2211?

20 A. Yes, it is.

21 Q. Thank you.

22 And what does this information disclose?

23 A. So this discloses Dr. Feldman's information on his
24 prescribing of Periostat. Note that it lists his name and
25 address and his speciality.

Stafford - direct

1 If you look at Column S, this represents
2 the number of new prescriptions that were dispensed in March
3 of the year 2000. 1.042 represents the number of projected
4 prescriptions that were dispensed during that month.

5 If we look further on in the spread sheet,
6 we can see in Columns AZ and BB a listing of the total
7 prescriptions that were supplied in two months, including
8 April 2000 and June of 2000. And, again, total
9 prescriptions represent the sum of new prescription and
10 refills.

11 In this case, since we don't see any new
12 prescriptions in April and June, the data represented in
13 columns AZ and BB represent in their entirety refills that
14 were dispensed at a pharmacy.

15 Q. And what opinion --

16 THE COURT: Hold on a second, counsel.

17 MS. RUPERT: Your Honor, I would like to object
18 to Dr. Stafford's testimony regarding this alleged refill
19 prescription. The refill prescription is addressed nowhere
20 in Dr. Stafford's report.

21 THE COURT: The objection is noted.

22 BY MS. WESTIN:

23 Q. Dr. Stafford, to ask you again, is this the
24 information that's presented in this slide, is it in
25 DTX-2211?

Stafford - direct

1 A. Yes, it is.

2 Q. And what opinion, if any, did you draw from this data
3 regarding Dr. Feldman?

4 A. Based on these data, it is my opinion that a
5 prescription for Periostat written by Dr. Feldman was
6 dispensed at a pharmacy March 2000.

7 Q. And how did you reach this conclusion?

8 A. This conclusion was reached on the basis of the IMS
9 Health Periostat data.

10 Q. Dr. Stafford, can you please tell us again whether or
11 not the 1.042 could ever represent a prescription that was
12 not written by Dr. Feldman?

13 A. In all cases, the presence of a projection means that
14 there actually was a prescription dispensed at the pharmacy.
15 In no case would a projection appear that was not based on
16 a prescription that was written and filled in the first
17 place.

18 MS. WESTIN: Can we turn to the next slide,
19 please?

20 BY MS. WESTIN:

21 Q. Can you please tell us what your next opinion is?

22 A. It is my opinion that the Periostat prescription
23 written by Dr. Feldman and filled March 2000 is likely the
24 same prescription represented in Dr. Feldman's patient
25 record.

Stafford - direct

1 Q. Can you please turn to DTX-1559 in your binder? And
2 is this Dr. Feldman's patient record?

3 A. Yes, it is.

4 Q. Did you review this patient record?

5 A. I did.

6 Q. Now, what is in this next slide?

7 A. This is a slide I prepared which displays the patient
8 record as well as several details. I've also included the
9 Column S from the previous slide.

10 Q. And what can you tell us about the patient record and
11 the IMS Health Periostat prescription data?

12 A. This record shows Dr. Feldman's prescribing of
13 Periostat for rosacea. This visit occurred on February
14 19th, 2000. And on this record, we see Dr. Feldman's report
15 of the patient's presented symptoms, his findings on
16 physical exam, and his diagnosis of rosacea. We also see
17 his rationale for selecting Periostat based on its
18 anti-inflammatory effect with reduced risk of side
19 effect.

20 We also see that Dr. Feldman supplied the
21 patient with the prescription for Periostat at 20 milligrams
22 to be taken -- to be taken orally twice per day. He
23 supplied 180 units or a 90-day supply and also provided the
24 patient with one refill.

25 Q. Do you have an opinion regarding this patient record

Stafford - direct

1 and the IMS Health data that you reviewed?

2 A. Yes. Given the IMS prescription data on Periostat
3 and this patient record, I believe it is likely that the
4 patient represented in this patient record of Dr. Feldman's
5 is the same patient and prescription that shows up in the
6 IMS Health Periostat data.

7 Q. And what is the basis for your opinion?

8 A. I base this opinion on the nature of the IMS Health
9 Periostat data, the prescription that Dr. Feldman has made
10 here, as well as my experience with the IMS Health data,
11 which suggests that it's not unusual for a dispensing of a
12 prescription to follow some time after the initial
13 prescription itself.

14 Q. Is there an alternative explanation available
15 regarding the filled Periostat prescription written by Dr.
16 Feldman and recorded by IMS Health?

17 A. Yes. Although perhaps less likely, the Periostat
18 data from IMS Health could represent a second patient that
19 Dr. Feldman provided Periostat to. In either case, the IMS
20 Health Periostat data indicates that March of 2000, a new
21 prescription written by Dr. Feldman was filled at a pharmacy
22 that provides information to IMS Health.

23 MS. WESTIN: Thank you, Dr. Stafford.

24 THE COURT: Cross-examination.

25 CROSS-EXAMINATION

Stafford - cross

1 BY MS. RUPERT:

2 Q. Good morning, Dr. Stafford.

3 A. Good morning.

4 Q. To start, I have a question about your giant binder,
5 which has been marked as DTX-1842. You have that there?

6 A. Yes, I do.

7 Q. Does it say rosacea anywhere in that giant binder?

8 A. No, it does not.

9 Q. Does it say the name of the alleged Feldman patient
10 anywhere in that giant binder?

11 A. No.

12 Q. You are not an expert in the treatment of rosacea;
13 correct?

14 A. Correct.

15 Q. You are not an expert in the treatment of
16 dermatological conditions; correct?

17 A. Yes.

18 Q. In fact, you are not even certified in dermatologic
19 practice; correct?

20 A. Yes.

21 Q. At the time you submitted your report in this case
22 regarding Dr. Feldman's alleged Periostat prescription, you
23 had not even reviewed Dr. Feldman's deposition transcript;
24 isn't that right?

25 A. That is incorrect.

Stafford - cross

1 Q. All right. Let me hand you a copy of your
2 deposition.

3 MS. RUPERT: May I approach, your Honor?

4 THE COURT: You may.

5 (Deposition transcript handed to the witness
6 and the Court.)

7 BY MS. RUPERT:

8 Q. All right. Do you have your deposition there?

9 A. Yes, I do.

10 Q. Okay. Let's turn to Page 61?

11 MS. RUPERT: If we could pull that up on the
12 screen.

13 BY MS. RUPERT:

14 Q. At your deposition, were you not asked the following
15 questions and did you not give the following answers:

16 "Question: Why don't you know whether it would
17 have been reasonable for you to review a transcript before
18 rendering your opinions and your expert report?

19 "Answer: At the time of my report, I had no
20 information as to whether there were differences between the
21 deposition report and the declaration of Dr. Feldman.

22 "Question: Weren't you curious?

23 "Answer: No, I was not particularly curious."

24 That's what you said at your deposition; is that
25 right?

Stafford - cross

1 MS. WESTIN: Your Honor, this is an issue.

2 THE COURT: Overruled. He can answer.

3 BY MS. RUPERT:

4 Q. That was your testimony at deposition; right, sir?

5 A. I'm unable to determine whether I was referring to
6 reviewing Dr. Feldman's deposition prior to preparing my
7 report or prior to preparing -- to providing my deposition.

8 Q. Did you not give the testimony that's up on that
9 board, sir?

10 A. Yes. At the time of my reported, I had not reviewed
11 Dr. Feldman's deposition. At the time of my deposition, I
12 had, in fact, reviewed that deposition.

13 Q. So earlier today, you testified about the Li
14 publication and that's DTX-2218 in support of your opinions
15 regarding off label use of Periostat; correct?

16 A. Yes.

17 Q. But you would agree with me, wouldn't you, that the
18 small number of dermatologists used in the Li study is a
19 shortcoming of that study; correct?

20 A. No.

21 Q. Let's turn back to your deposition. Please turn to
22 Page 139. And if I could direct your attention to line 5.

23 At your deposition, were you not asked the
24 following questions and did you not give the following
25 answers:

Stafford - cross

1 "Question: Do you think the small number of
2 academic dermatologists used by Li to be considered a
3 shortcoming of that study?

4 "Answer: Yes."

5 That was your testimony at deposition; right?

6 A. Yes, it was.

7 Q. Of the drugs discussed as being prescribed off label
8 in the Li study, doxycycline was never mentioned; is that
9 right?

10 A. Correct.

11 Q. Let's turn to figure three in the Li study. That's
12 DTX-2218?

13 MS. RUPERT: Could you put that on the board?

14 BY MS. RUPERT:

15 Q. I'd like to direct your attention to figure 3 of that
16 study on page 1452.

17 Now, wouldn't you agree that in that study, Li
18 also found that, and I quote the last sentence of figure 3,
19 "As might be expected, most dermatologists did not use drugs
20 for a condition that they did not believe to be FDA
21 approved."

22 That's what that says there; right?

23 A. Yes.

24 Q. Now, earlier today, you also testified about the
25 Sugarman publication, and that's DTX-2214, in support of

Stafford - cross

1 your opinion that of all prescriptions -- in support of your
2 opinion that 73 percent of all prescriptions for rosacea
3 were written off label; is that correct?

4 A. Yes.

5 Q. And the Sugarman study evaluated data from 1990
6 through 1997; correct?

7 A. Yes.

8 Q. Periostat was not even launched until 1998; is that
9 correct?

10 A. Yes, that is correct.

11 Q. So the Sugarman publication did not include Periostat
12 in its analysis; right?

13 A. Yes.

14 Q. Now, Dr. Stafford, you have found an error in IMS
15 data before; correct?

16 A. Yes, I have.

17 Q. And you testified today that the IMS data that we've
18 marked as DTX-2211 shows that at least one new Periostat
19 prescription was filled by one of Dr. Feldman's patients
20 March 2000; correct?

21 A. Yes.

22 Q. And you believe that it is likely that this Periostat
23 prescription was filled by the same patient that was
24 referenced in Dr. Feldman's patient record, DTX-1559;
25 correct?

Stafford - cross

1 A. Because there is no patient identifying information
2 either in the Periostat data provided by IMS Health, nor in
3 Dr. Feldman's patient record, it's impossible to know with
4 certainty that the same patient represented in Dr. Feldman's
5 record is, in fact, the patient that filled that
6 prescription in March of 2000. However, I believe it is
7 likely that this patient is, indeed, the same patient.

8 Q. But you would agree, wouldn't you, that, in fact, it
9 is impossible to directly link the prescription that is
10 referenced in Dr. Feldman's medical record and the
11 individual who filled the prescription in the IMS data;
12 correct?

13 A. As I said, it's impossible to know with certainty
14 that those are the same patient. However, because of the
15 nature of the IMS Health and the information provided by Dr.
16 Feldman, it's my opinion that it's likely that those are,
17 indeed, the same patient.

18 Q. But it's only likely because there are no patient
19 identifiers in the IMS data; right?

20 A. Yes. As I said, both in Dr. Feldman's medical
21 record, the patient identifying information has been crossed
22 out and in the IMS Health Periostat data, that data never
23 contains information specifically identifying the patient
24 who has filled the prescription.

25 Q. Right. It's impossible to make that link because all

Stafford - cross

1 patient identifiers are scrubbed from the raw data before it
2 is released to IMS; correct?

3 A. Again, it's impossible to know with certainty
4 because, as you say, the patient identifiers are not
5 transmitted by the pharmacy to IMS Health.

6 Q. And information related to patient diagnosis is also
7 not available in the type of IMS data you reviewed in this
8 case; right?

9 A. That's correct.

10 Q. And even Dr. Feldman himself doesn't know if the
11 patient referenced in his medical record, DTX-1559, filled
12 the Periostat prescription; right?

13 A. Yes.

14 Q. All right. Let's turn to DDX-114, which you talked
15 about in your testimony today.

16 Would you pull up the slide, please?

17 All right. And there you reference 1.055
18 projected refill prescriptions written by Dr. Feldman;
19 correct?

20 A. Yes, correct.

21 Q. But IMS provided no patient identifying information
22 there either; right?

23 A. No information is ever transmitted from the pharmacy
24 to IMS Health which would allow users to specifically
25 identify patients who are filling these prescriptions.

Stafford - cross

1 Q. And information related to patient diagnosis is also
2 not available for that refill prescription through IMS;
3 correct?

4 A. Yes.

5 Q. Okay. Let's now turn back to DDX-106 which you also
6 testified about today.

7 You have listed some bullet points there towards
8 the bottom regarding what IMS Health data provides; right?

9 A. Correct.

10 Q. But I want to talk about what is not there. You did
11 not list patient identifying information because as we
12 discussed, IMS does not provide that; right?

13 A. Yes.

14 Q. And you also did not list information regarding
15 patient diagnosis because that is also not provided by IMS;
16 right?

17 A. That is correct.

18 Q. So, Dr. Stafford, also today you testified that
19 doctors were prescribing Periostat off-label for the
20 treatment of rosacea prior to April 2000; right?

21 A. Yes.

22 Q. But you would agree, wouldn't you, that not all
23 off-label use of Periostat is for treatment of rosacea;
24 correct?

25 A. Yes.

Stafford - cross

1 Q. In fact, at your deposition, you were not able to
2 name a single dermatologist who prescribed Periostat
3 off-label for any use prior to April 2000 other than
4 possibly Dr. Feldman's alleged prescription; right?

5 A. At the time of my deposition, I had not reviewed and
6 memorized the names of the physicians. However, I did know
7 that 67 of those physicians listed in the DTX-1842 were
8 dermatologists who prescribed Periostat prior to April of
9 2000 either as new or as refill prescriptions, and that
10 those prescriptions had been filled at a pharmacy that
11 records data to IMS Health.

12 MS. RUPERT: Why don't we go to a video clip to
13 see what you said at your deposition. Could you please pull
14 up the video clip?

15 "Question: Okay. And can you name other than
16 Dr. Feldman a single dermatologist who was prescribing
17 Periostat off label prior to April 2000?

18 "Answer: No.

19 BY MS. RUPERT:

20 Q. And that's what you said at your deposition; right?

21 A. Yes. I said that I could not provide the name of
22 dermatologists who were prescribing Periostat prior to
23 April 2000.

24 Q. Okay. Let's turn back to DDX-109.

25 Can you say, with absolute certainty, that all

Gilchrest - direct

1 of the dermatologists that you listed here were prescribing
2 Periostat off-label?

3 A. It's impossible to say for sure what indications
4 these physicians were using Periostat for.

5 Q. Okay. And you can also not name, with certainty, a
6 single dermatologist who prescribed Periostat for the
7 treatment of rosacea prior to April 2000; correct?

8 A. Again, because the IMS Health data is lacking
9 information on diagnosis, it's impossible to know with
10 certainty whether any of these physicians were prescribing
11 Periostat for rosacea prior to April 2000.

12 MS. RUPERT: I have no further questions, your
13 Honor.

14 THE COURT: Any redirect?

15 MS. WESTIN: No, your Honor.

16 THE COURT: Okay. You can step down, doctor.
17 Thank you.

18 Mylan may call its next witness.

19 MR. STEUER: Mylan calls Dr. Barbara Gilchrest.

20 BARBARA GILCHREST, having been first duly sworn,
21 was examined and testified as follows:

22 THE COURT: Good morning, Dr. Gilchrest.

23 THE WITNESS: Good morning.

24 DIRECT EXAMINATION

25 BY MR. STEUER:

Gilchrest - direct

1 Q. Good morning, Dr. Gilchrest.

2 A. Good morning.

3 Q. Would you please introduce yourself to the Court?

4 A. I'm Barbara A. Gilchrest here as a witness for Mylan.

5 Q. And did you prepare some slides with the assistance
6 of counsel?

7 A. I did.

8 Q. And did counsel screw up one of the slides, as we'll
9 get to?

10 A. Yes. Only one that I know of.

11 Q. Dr. Gilchrest, let's go to DDX-202. And I wonder if
12 you could briefly describe your educational background to
13 the Court?

14 A. Yes, I have a bachelor's of mathematics from MIT and
15 an MD degree from the Harvard Medical School.

16 I trained in Internal Medicine and then in
17 dermatology at the Harvard affiliated hospitals; and I
18 served research fellowships in Photobiology, Photomedicine
19 and Cell and Molecular Biology at MIT.

20 Q. Tell us about your current position.

21 A. I'm presently Professor and Chair Emeritus of the
22 Department of Dermatology at Boston University School of
23 Medicine.

24 Q. What are your responsibilities as such?

25 A. Presently, I see patients on a regular basis, and I

Gilchrest - direct

1 work with trainees both in clinical settings and on writing
2 and research projects.

3 Q. Do you currently hold any other academic or
4 professional positions?

5 A. I am a Dermatologist and Dermatologist-in-Chief
6 Emeritus at the Boston Medical Center in Boston, and I also
7 serve as the founder and Chief Medical -- Chief Scientific
8 Officer for a startup biotech company, SemaCo.

9 Q. And what sort of technology does SemaCo work with?

10 A. SemaCo has licensed from Boston University the
11 intellectual property that arose over the years in my
12 laboratory work regarding treatment of skin disorders,
13 cancer prevention and cancer therapy.

14 Q. Dr. Gilchrest, are you a board certified physician?

15 A. I am. I'm certified in internal medicine and in
16 dermatology.

17 Q. How long have you been practicing as a dermatologist?

18 A. 35 years.

19 Q. Have you ever seen a patient with acne or rosacea?

20 A. I see many, many patients with acne and rosacea.
21 It's one -- those are among the most common dermatologic
22 disorders. I would estimate over the 35 years that I have
23 had literally tens of thousands of visits for those
24 diagnoses.

25 Q. Have you participated in the training of doctors or

Gilchrest - direct

1 fellows in the dermatology field with respect to the
2 treatment of acne or rosacea?

3 A. Yes. From the beginning of my career, I've been
4 involved in training medical students, dermatology residents
5 and physicians in other fields as well as graduate
6 physicians in the management of these diseases. I did that,
7 do that at the bedside, if you will, in the clinic on a
8 regular basis.

9 I also, for 23 years, served as the director of
10 the dermatology residency program at Boston Medical Center
11 where I was responsible for assuring that all of our
12 trainees were properly knowledgeable about diagnosis and
13 management of all dermatologic diseases and certainly
14 including acne and rosacea.

15 Q. Have you ever received any recognition or awards for
16 your professional work?

17 A. Yes, I have. I've been named as among the best
18 doctors in America since 1996. I'm a fellow of the American
19 Academy of Sciences. I'm an elected member of the National
20 Academies of Science. I'm among the leading physicians of
21 the world. I've been given many named lectureships and
22 awards from societies and dermatologic organizations.

23 Q. Have you participated in professional organizations
24 in the dermatology field?

25 A. Yes, I have. I've been very active in organized

Gilchrest - direct

1 dermatology.

2 I've served as the President for the Society of
3 Investigative Dermatology, for the Association of Professors
4 of Dermatology, for the Women's Dermatologic Society. I've
5 been on the board of the American Academy of Dermatology,
6 the Society For Investigative Dermatology, and a number of
7 other organizations.

8 Q. Have you ever written anything about dermatology?

9 A. Publish or perish. I have over 400 publications,
10 including original research reports, clinical studies,
11 clinical reviews, chapters, editorials, a number of
12 publications.

13 Q. Is there a book called Fitzpatrick's Dermatology in
14 General Medicine?

15 A. Yes. Most people would consider this to be the
16 leading textbook in dermatology. I served as an editor for
17 that textbook for the last I think eight years.

18 Q. Have you ever peer-reviewed scientific works for
19 publication in the dermatology field?

20 A. Yes. I've been very active in peer review. I've
21 review for all major dermatologic and medical journals on a
22 fairly regular basis. I serve on the editorial board for a
23 large number of research and clinical publications; and I
24 was recently selected to be the editor in chief for the
25 Journal of Investigative Dermatology beginning next June.

Gilchrest - direct

1 Q. Have you ever invented anything?

2 A. Yes. In the course of my research work, our group
3 submitted a number of patent applications, and we have I
4 believe 10 separate patent families that have been granted.

5 MR. STEUER: May I approach with some binders?

6 THE COURT: You may.

7 (Binders passed forward.)

8 BY MR. STEUER:

9 Q. Dr. Gilchrest, can you take a look at what we have
10 marked in this binder as DTX-2135?

11 A. I'm sorry? 2?

12 Q. 2135.

13 A. Yes.

14 Q. Do you recognize this?

15 A. Yes, this is my curriculum vitae.

16 MR. STEUER: Your Honor, we offer DTX-2135.

17 MR. FLATTMANN: No objection.

18 THE COURT: It is admitted.

19 (DTX-2135 received into evidence.)

20 MR. STEUER: Your Honor, we offer Dr. Gilchrest
21 as an expert in the area of clinical dermatology with a
22 specific focus in the treatment of acne and rosacea.

23 MR. FLATTMANN: No objection.

24 THE COURT: She is so recognized.

25 BY MR. STEUER:

Gilchrest - direct

1 Q. Dr. Gilchrest, did we ask you to do something in this
2 case?

3 A. Yes. Mylan asked that I review the Ashley patents in
4 light of the present litigation and Mylan's intent to sell a
5 drug, a generic version of Oracea.

6 Q. And have you prepared a slide summarizing your
7 opinions?

8 A. Yes, I have.

9 MR. STEUER: All right. 203, please.

10 BY MR. STEUER:

11 Q. Is this the slide?

12 A. It is.

13 Q. What is your opinion?

14 A. It is my opinion that the asserted claims of the
15 Ashley patents are anticipated or obvious in view of
16 Dr. Feldman's personal use of Periostat to treat his rosacea
17 as well as his treatment of his patient's rosacea.

18 That the asserted claims of the Ashley patents
19 are anticipated or obvious in view of prior art involving
20 low dose tetracycline treatment of acne or rosacea.

21 That the claims are also obvious in view of the
22 use of low dose tetracycline to treat rosacea with Periostat
23 and the Periostat claims.

24 The asserted claims of the Ashley patents in my
25 opinion are obvious in view as well of prior art involving

Gilchrest - direct

1 ocular rosacea references. And,

2 Finally, I believe that there is no surprising
3 result or long-felt need for the Ashley patent claims.

4 MR. STEUER: All right. Let's go to DDX-204.

5 BY MR. STEUER:

6 Q. What did you consider in forming your opinions?

7 A. Yes. Those materials are listed on this slide. The
8 two Ashley patents, the '267 and '572 patents. The file
9 history for those patents, other documents that counsel
10 provided in that regard, as well as the understanding of one
11 of ordinary skill in the art in reviewing those documents.

12 I have also had an opportunity to review the
13 Court's claim construction. I've been informed by counsel
14 of applicable legal principles.

15 I've had an opportunity to review the documents
16 produced by the plaintiffs and those aspects of the
17 scientific and medical literature that pertain. I have also
18 looked at the plaintiffs' experts' opinions, depositions and
19 trial testimony. And,

20 Finally, my own personal education, background
21 and experience in this area.

22 Q. Do you know what the claims are in the Ashley patent
23 asserted here?

24 A. I generally know them. I would know them if I saw
25 them, yes.

Gilchrest - direct

1 Q. Did you prepare a slide --

2 A. I did.

3 Q. -- that lists them? All right.

4 Would you like to describe what we see here?

5 A. Yes. Perhaps I could read the independent claim 1 of
6 the '267 patent, which is a method of treating acne, which I
7 understand for purposes of this litigation is also rosacea,
8 in a human in need thereof comprising administering orally
9 or intravenously to said human an antibiotic tetracycline
10 compound in a sub-antibacterial amount that reduces lesion
11 count, said amount being 10 to 80 percent of the
12 antibacterial effective amount, wherein the tetracycline
13 compound is administered long term, without administering a
14 bisphosphonate compound.

15 And the dependent claims that are being asserted
16 are listed below that.

17 MR. STEUER: All right. Let's go to the next
18 slide.

19 BY MR. STEUER:

20 Q. And what is DDX-206?

21 A. Yes. These are the asserted claims of the '572
22 patent, which differ primarily in the independent claim 1 as
23 pertaining to the papules and pustules of rosacea
24 specifically. It is otherwise essentially identical in
25 wording.

Gilchrest - direct

1 Q. Okay. And there are some dependent claims asserted
2 there?

3 A. Yes. The dependent claims pertain specifically to
4 the use of doxycycline, the doxycycline monohydrate in
5 particular, and in a dose of 40 milligrams daily.

6 Q. All right. And on 207 do we have some more claims?

7 A. Yes, there is a second independent claim 20 which is
8 directed to a method for treating papules and pustules of
9 rosacea in a human in need thereof comprising administering
10 orally to said human a hydrate of doxycycline in an amount
11 that is effective to treat the papules and pustules but with
12 no substantial antibiotic activity in an amount of 10 to
13 80 percent of the antibiotic amount, wherein the hydrate of
14 doxycycline is administered in an amount that results in no
15 reduction of skin microflora during a six-month treatment,
16 said method not comprising administering a bisphosphonate
17 compound.

18 Q. Do the asserted claims have any dependent claims?

19 A. It does. Those are listed below. They specify
20 specific forms of doxycycline in the dose of 40 milligrams
21 as well as a composition that is sustained release
22 administered once a day.

23 Q. Dr. Gilchrest, when you first reviewed the Ashley
24 patents, were you surprised?

25 A. I was surprised it was a patent, but I wasn't

Gilchrest - direct

1 surprised at the method of treatment that was described
2 there.

3 Q. Why not?

4 A. Because it has been my teaching and experience over
5 many, many years that low dose tetracyclines are effective
6 in treating acne and rosacea, particularly rosacea, and
7 that doxycycline is among those antibiotics and that, in
8 particular, a commercially available 50 milligram dose of
9 doxycycline had been widely used by myself and others with
10 very good results.

11 Q. Have you reviewed the Court's claim construction
12 order for the Ashley patents?

13 A. I have.

14 Q. In forming the opinions you are going to give today,
15 did you apply the claim construction issued by the Court in
16 this case?

17 A. I have.

18 Q. Have you also reviewed the Court's preliminary
19 injunction ruling on the Ashley patents?

20 A. I have.

21 Q. Will you be relying on any new prior art references
22 that were not presented in your expert report today?

23 A. No, I will not.

24 Q. I'd like to briefly turn to your experience with
25 rosacea patients. Have you ever treated rosacea patients

Gilchrest - direct

1 with tetracycline compound?

2 A. Yes. Many, many times.

3 Q. Which tetracycline products do you prescribe to your
4 rosacea patients?

5 A. Many years ago, probably primarily tetracycline
6 itself, but in more recent decades, doxycycline and
7 sometimes minocycline.

8 Q. What doses of doxycycline do you prescribe for
9 rosacea?

10 A. Most commonly, 50 or 100 milligrams per day.

11 Q. What is your experience in using doxycycline to treat
12 rosacea?

13 A. It is my experience that it is often dramatically
14 helpful at the doses I mentioned and that patients generally
15 tolerate doxycycline at those doses very well. It is
16 uncommon, very uncommon in my practice for patients to
17 experience adverse effects either gastrointestinal upset or
18 phototoxicity.

19 Q. Now, there was, you heard discussion here yesterday
20 about phototoxicity from doxycycline above 40 milligrams.
21 Is this something that you experienced or that you are
22 familiar with?

23 MR. FLATTMANN: Objection, your Honor. Outside
24 the scope of the expert report.

25 THE COURT: The objection is noted.

Gilchrest - direct

1 You can answer the question.

2 THE WITNESS: Yes. I did hear Dr. Webster
3 describe problems with treating his patients during the
4 summer due to phototoxicity reactions. This is not
5 something that my patients report to me, and I think I
6 mentioned that I had spent an entire year studying
7 specifically photomedicine, photobiology, effects of UV on
8 skin; and in that context, I learned a great deal about
9 phototoxicity, and over the years I frequently hear from
10 colleagues or have patients referred to me from colleagues
11 because of phototoxicity problems. It is extremely rare to
12 encounter a patient experiencing phototoxicity from
13 doxycycline prescribed for the indication of rosacea.

14 Q. Well, what's the frequency of administration of
15 doxycycline that you generally prescription?

16 A. The route of administration? Oral.

17 Q. Not the route, the frequency.

18 A. The frequency? Usually, I use a daily
19 administration.

20 Q. Okay. Why do you prescribe a once daily dosage form?

21 A. Because it is easier for the patient and it improves
22 compliance.

23 Q. When did you begin to prescribe once daily dosage
24 forms for rosacea patients?

25 A. When possible, from the very beginning, during my

Gilchrest - direct

1 residency, and almost exclusively in the past say 20 years.

2 Q. Do you prescribe Oracea to patients?

3 A. Rarely.

4 Q. Dr. Gilchrest, do you know what Periostat is?

5 A. I do. Periostat is doxycycline 20-milligram
6 administered twice daily as already mentioned this morning
7 for the indication of an adjunct treatment for
8 periodontitis.

9 Q. Let's look at slide 208. Is Periostat relevant to
10 the Ashley patents?

11 A. It is. Periostat is mentioned as a preferred
12 embodiment in the Ashley patents.

13 Q. And that would be at -- in the '267 patent at column
14 5, 63 to 67?

15 A. I believe so.

16 Q. All right. And that's, for the record, that's in
17 your binder at Defendants' Trial Exhibit 1007, but I believe
18 the patent has already been admitted.

19 How was Periostat used in the Ashley patents?

20 A. Periostat was --

21 Q. Go ahead.

22 A. Thank you.

23 As shown on this slide, example 38 in the
24 specification for the Ashley patent describes a study
25 involving 60 patients, 30 of whom received Periostat,

Gilchrest - direct

1 20 milligrams twice daily for treatment of acne vulgaris.

2 And in this study, in example 38, they report that there was
3 a modest but statistically significant improvement in the
4 papules and pustules of those patients, and that they also
5 examined before and after a six-month treatment period skin
6 swabs and found no difference in the microflora recovered
7 from those skin swabs after the six-month treatment with
8 Periostat.

9 Q. Can you look in your binder as what has previously
10 been admitted as defendant's trial Exhibit 1559?

11 A. Yes.

12 Q. Do you know what this is?

13 A. This is a copy of the note from Dr. Feldman's office
14 record, his February 19, 2000 visit.

15 Q. And are you familiar with Dr. Feldman's testimony in
16 this case?

17 A. Yes, I am.

18 Q. All right. Let's turn, if we may, to your first
19 opinion. What is this opinion again?

20 A. Yes. The asserted claims of the Ashley patents are
21 anticipated or obvious in view of Dr. Feldman's use of
22 Periostat to treat his own and his patient's rosacea.

23 MR. STEUER: If we could go to DDX-211.

24 BY MR. STEUER:

25 Q. Can you give us the basis for your opinion, Dr.

Gilchrest - direct

1 Gilchrest?

2 A. I have been informed by counsel that a doctrine in
3 the law is that which infringes if later would anticipate if
4 earlier. And I understand that Mylan is being accused of
5 inciting to infringe by encouraging physicians to prescribe
6 a generic version of Oracea to use in exactly the way that
7 Dr. Feldman treated himself and his patient.

8 Q. Now, do you have an opinion as to whether Dr.
9 Feldman's use and prescribing of Periostat met the
10 limitation of a sub-anti-bacterial dose and the limitation
11 of no reduction in skin microflora?

12 A. Yes. As described, for example, in the Periostat
13 package insert, this dose of Periostat does not alter
14 bacterial flora, at least in the mouth, and is considered
15 sub-antibiotic and it's not an antibiotic dose.

16 Q. What about the skin microflora?

17 A. Skin microflora, also as -- are also not affected.

18 Q. Now, do you have an opinion as to whether Dr.
19 Feldman's use in prescribing of Periostat renders obvious
20 any elements of the -- of the '267 or 572 patent?

21 A. Yes. In my opinion, it renders all of them, many of
22 the asserted claims obvious, yes.

23 Q. And why is that?

24 A. Do we have that on a subsequent slide, on the next?
25 If we through the asserted claims --

Gilchrest - direct

1 Q. All right.

2 A. -- I will comment on that.

3 Q. So have you prepared a chart?

4 A. Yes.

5 Q. As to the claims?

6 A. Yes, I have.

7 Q. Would you like to go through this for the Court?

8 A. Yes. This is the independent claim 1 of the '267
9 patent, and the elements of that claim are specified on the
10 left side of the slide.

11 First, a method of treating acne in a human
12 in need thereof. And, again, for the purpose of this trial,
13 acne and rosacea are considered to be the same disorder, and
14 Dr. Feldman, according to his deposition, treated his own
15 rosacea.

16 The second element, administering orally or
17 intravenously to said human an antibiotic tetracycline,
18 and Periostat is administered orally, and he used it in that
19 way.

20 Third, in a sub-antibacterial amount that
21 reduces lesion count. And Periostat, as described in the
22 Ashley patent, is an especially preferred embodiment and
23 that it is administered in a sub-anti-bacterial amount
24 according to the patent and this is the way Dr. Feldman used
25 it.

Gilchrest - direct

1 Next, that the said amount be 10 to 80 percent
2 of the anti-bacterial effective amount, and as specified in
3 the Ashley patents, 40 milligrams of doxycycline is
4 80 percent of the lowest exemplary anti-bacterial effective
5 amount listed in that patent specification.

6 Next, wherein the tetracycline compound is
7 administered long term, which I understand the parties have
8 agreed is more than eight to ten days. And Dr. Feldman has
9 testified that he used the Periostat for six to
10 seven months.

11 Q. Was that six to seven months?

12 A. I mean -- excuse me. Seven to eight months. And
13 without administering of bisphosphonate compound. And Dr.
14 Feldman has testified that he did not use a bisphosphonate
15 compound.

16 Q. All right. Do you believe that Dr. Feldman's
17 Periostat use anticipates any dependent claims?

18 A. Yes, I do.

19 Q. Okay. And which claims would that be?

20 A. I believe I have a slide.

21 Q. First of all, why don't we go through claim 1 of the
22 '572 patent as well.

23 A. All right. As mentioned, the '572 patent is very
24 similar to the '267 patent except that it is a method for
25 treating papules and pustules of rosacea rather than

Gilchrest - direct

1 treating acne, and Dr. Feldman has specifically testified
2 that he had papules and pustules of rosacea.

3 The other claims are essentially the same except
4 for the highlighted claim toward the bottom, which requires
5 administration in an amount that results in no reduction of
6 skin microflora during the six-month treatment.

7 And we know from the patent specification that
8 the Periostat as used by Dr. Feldman would not have resulted
9 in a decrease in skin microflora, and he used the drug for
10 six to seven months.

11 Q. All right. Can we talk about your opinions on the
12 validity of certain dependent claims of the Ashley patents
13 in view of Dr. Feldman's testimony?

14 A. Yes. I believe those were shown in the next.

15 Q. Next slide.

16 A. So listed here are the dependent claims, which I
17 believe -- do I have a copy of the patent claims myself to
18 refer to?

19 Q. You do, but we can also put the claims up next to the
20 screen, if that would be helpful.

21 A. Yes. I believe claim 22 refers specifically to
22 treatments of papules and pustules. And that is, again,
23 what Dr. Feldman was -- ah. Thank you.

24 Yes. No. Claim 22 is a method according to
25 claim 20, the treatment of papules and pustules, wherein a

Gilchrest - direct

1 hydrate of doxycycline is used, and that is the preparation
2 used by Dr. Feldman.

3 Claim 23, method according to claim 1, wherein
4 the tetracycline compound is in an amount of 40 to
5 70 percent of anti-bacterial effective amount, and 40
6 milligram is 40 percent of a hundred milligram, as in the
7 patent specification.

8 Claim 26, method according to claim 24, wherein
9 the lesion of papules and pustules, which, indeed, is what
10 Dr. Feldman was treating in himself.

11 28 is a method of claim 1, wherein the
12 sub-antibacterial amount is an amount that results in no
13 reduction of skin microflora during a six-month treatment
14 period, which would have been an inherent property because,
15 again, Periostat was disclosed not to affect skin microflora
16 over a six-month period.

17 And claim 30, method according to claim 26,
18 wherein the antibacterial amount is an amount that results
19 in no reduction of skin microflora, which is also met in my
20 opinion.

21 Q. Okay. And let's look at the dependent claims from
22 the '572 patent that you think are anticipated.

23 A. Right. So claim 12 of that patent -- thank you -- is
24 the method of claim 1, wherein the tetracycline is
25 doxycycline or pharmaceutically acceptable salt thereof,

Gilchrest - direct

1 and, indeed, Periostat is doxycycline.

2 And in claim 14, the method of claim 12, wherein
3 the doxycycline is administered in an amount of
4 40 milligrams and 20 milligrams twice daily, 40 milligrams
5 per day.

6 Q. All right. Now, why do you think that dependent
7 claim 14 is anticipated by Feldman? Did he use a salt
8 thereof?

9 A. He did. Monohydrate salt. No -- yes. Monohydrate
10 salt.

11 Q. Okay. Well, is there a difference between
12 monohydrate and doxycycline hyclate, which is Periostat?

13 A. They are different chemical entities, but it is known
14 in the art that they are bio -- they have equal
15 bioavailability and equal actions in the body.

16 Q. Could you take a look at Defendants' Exhibit 1694?

17 A. Yes. I think we have a slide supporting that.

18 Q. Let's go to slide 224. First, let's take a look at
19 the exhibit, 1694.

20 Do you have that?

21 A. Yes. This is -- 1694 is a review article by Howard
22 Maibach from 1991 regarding second generation tetracycline.
23 It's a dermatologic overview, clinical uses in pharmacology.

24 And Dr. Maibach in this paper makes the point
25 that no difference has been found in the absorption or

Gilchrest - direct

1 bioavailability of these two forms of doxycycline that are
2 represented by Periostat and Oracea.

3 Q. Is doxycycline hyclate the same as the hydrochloride
4 salt of doxycycline?

5 A. That's the hyclate. The hydrochloride salt is the
6 hyclate and the monohydrate is converted into hyclate in the
7 stomach.

8 MR. STEUER: Your Honor, I move the admission of
9 Defendants' Trial Exhibit 1694.

10 MR. FLATTMANN: No objection, your Honor.

11 THE COURT: Admitted.

12 (DTX-1694 was admitted into evidence.)

13 BY MR. STEUER:

14 Q. Why is equivalency and bioavailability or absorption
15 between doxycycline monohydrate and hyclate important?

16 A. It's important because it would tell one of normal
17 skill in the art that these drugs would behave identically
18 in the body.

19 Q. Now, there's a -- there are claims in the patent that
20 refer to sustained release or once daily dependent claims in
21 the '572 patent; correct?

22 A. Yes.

23 Q. And do you have a slide discussing your opinion on
24 these --

25 A. Yes.

Gilchrest - direct

1 Q. -- dependent claims?

2 A. Yes. Yes. I believe that's the next slide, and it
3 is my opinion that these dependent claims are also obvious
4 in that the difference between the two compositions were
5 known to one to make no real difference prior to the
6 submission of the Ashley patents.

7 As shown on this slide, there are two U.S.
8 patents that were issued in 1993, 1994 that specifically
9 describe sustained release of antibiotics such as
10 doxycycline hyclate in order to allow for a single daily
11 dosing as well as the second patent noted on this slide
12 describes controlled release of active medication that is
13 particularly noted, particularly effective when comprised of
14 relatively low dose for that medication.

15 Q. Dr. Gilchrest, could you take a look in your binder
16 at Defendants' Trial Exhibits 1996 and 2005?

17 A. Yes.

18 Q. Are these the patents of which you spoke?

19 A. Yes, they are.

20 MR. STEUER: Your Honor, I move the admission of
21 1996 and 2005, Defendants' Trial Exhibits.

22 MR. FLATTMANN: No objection.

23 THE COURT: They're admitted.

24 (Defendants Trial Exhibits 1996 and 2005 were
25 admitted into evidence.)

Gilchrest - direct

1 BY MR. STEUER:

2 Q. Let me ask you to take a look again -- let's move to
3 226. Ask you to take a look again at Dr. Feldman's patient
4 record.

5 A. Yes.

6 Q. What is disclosed here, generally?

7 A. A method of treating rosacea by -- with Periostat
8 20 milligrams twice daily, administered because of its
9 anti-inflammatory effects, and diminished risk of side
10 effects to be used for a period of six months with an
11 initial prescription for three months, refillable for a
12 second three months.

13 Q. Have you formed an opinion regarding whether Dr.
14 Feldman's prescribing of Periostat to his patient
15 invalidates the asserted claims of the Ashley patents?

16 A. I believe that it does.

17 Q. And is the basis for your opinion any different from
18 your opinion with respect to Dr. Feldman's own use of
19 Periostat?

20 A. No. It is my opinion that both uses anticipate the
21 Ashley patents.

22 Q. And do you believe that Dr. Feldman's prescribing of
23 Periostat invalidates the same independent and dependent
24 claims as his own use?

25 A. Yes.

Gilchrest - direct

1 Q. Now, did Dr. Feldman testify as to why he prescribed
2 Periostat to his patient?

3 A. He did.

4 Q. And what did he say, as you recall?

5 A. As I recall, he specified that he had been made aware
6 that this, through a presentation at a continuing medical
7 education meeting, that such treatment would be helpful. He
8 was also aware that tetracycline had anti-inflammatory
9 effects at sub-antibacterial doses, and that he, therefore,
10 understood that this would be an effective treatment for his
11 patient.

12 Q. Dr. Gilchrest, as a physician, is there an ethical
13 obligation to prescribe medications that you expect to help
14 the patient?

15 A. There is.

16 Q. And is there also a practice among physicians to
17 discuss effective therapies?

18 A. In my experience, it is very common for physicians to
19 discuss the responsive patient's specific medications or
20 complications that they might experience or their general
21 results with approaching diseases in certain ways. But this
22 is done without specifically identifying the patients
23 involved, and so is considered to be both ethically and
24 legally completely appropriate.

25 Q. Now, if we could turn to Page 236, DDX-236.

Gilchrest - direct

1 Now, you believe that the asserted claims of the
2 '572 patent are obvious in view of Dr. Feldman's patient
3 record; is that right?

4 A. Yes, I do.

5 Q. And the reason is?

6 A. As listed on this slide, the doxycycline hydrate,
7 dependent claims 13 and 20 and 21 and 23 I would believe
8 render the treatment obvious in view Maibach because of the
9 equivalency of the two forms of tetracycline. That based on
10 the patents just submitted in evidence, that the idea of
11 sustained release or once daily dosing, as specified in
12 claim 15, would have been obvious, and that sustained
13 release once daily doxycycline hydrate claims 24 and 26
14 would also be obvious in view of the Maibach review and the
15 patents that we've already discussed.

16 Q. Was the learning of Maibach generally known to people
17 of ordinary skill in the art as of 2000?

18 A. In my opinion, absolutely, yes. This was common
19 knowledge.

20 Q. And was the knowledge that doxycycline was suitable
21 to once a day or sustained release dosing known to persons
22 of ordinary skill in the art as of 2000?

23 A. In my opinion, this would be known, yes.

24 Q. And, Dr. Gilchrest, do you have an opinion as to
25 whether Dr. Feldman, in fact, treated his patient?

Gilchrest - direct

1 A. I do. Much has been made so far this morning about
2 the fact that he couldn't know if his patient actually
3 filled the prescription or if his patient actually took
4 every pill or the specifics of what happened after he wrote
5 the prescription and instructed his patient. However, it is
6 my opinion that the act of treating -- that treating a
7 patient consists of diagnosing that patient and prescribing
8 a therapy for that patient. When I treat patients, I never
9 really know whether they fill their prescriptions or take
10 their medicines. Unless they tell me they haven't, I
11 presume that they have, and that is in my experience the --
12 overwhelmingly the common outcome. Patients come to the
13 doctor in order to get better and treatment of a patient
14 consists in providing that patient with a prescription or
15 with instruction, instructions for use of medication or
16 specific regimen. It does not consist of following the
17 patient to the drugstore and their bathroom to be sure that
18 they are doing everything exactly as I have suggested.

19 Q. Dr. Gilchrest, do you have an opinion whether one of
20 ordinary skill in the art could have practiced the asserted
21 claims in the Ashley patent if given Dr. Feldman's patient
22 record?

23 A. In my opinion, that -- it is completely adequate for
24 practicing the method described in the Ashley patents.

25 Q. In your experience, are dermatologists amenable to

Gilchrest - direct

1 prescribing off label?

2 A. Absolutely, yes. I completely agree with the
3 testimony that Dr. Stafford has given, and in my own
4 experience, it is extremely common to prescribe off label
5 for virtually any dermatological condition, but certainly
6 including for rosacea.

7 And I might --

8 Q. Do you believe there are many dermatological
9 indications for Periostat?

10 A. Periostat as a sub-antibacterial dose of tetracycline
11 antibiotic would not be appropriate to use for any infection
12 indication for use of the tetracycline antibiotic, so all of
13 those would be excluded.

14 There are other disorders which might rarely be
15 considered for treatment with an antiinflammatory low dose
16 of a tetracycline, but they are relatively rare, much, much
17 less commonly seen than rosacea, which is seen in any
18 general dermatology practice daily.

19 Q. Dr. Gilchrest, let's turn to your second opinion.

20 And what is this opinion?

21 A. Yes, it is my opinion that the asserted claims of the
22 Ashley patents are anticipated and obvious in view of prior
23 art, low dose tetracycline use.

24 Q. All right. And what is the basis for this opinion?

25 A. There are a number of papers in the prior art that

Gilchrest - direct

1 speak to use of low dose tetracyclines. Yes, here. And
2 there are comments throughout the prior art literature to
3 the effect that acne and rosacea were not infectious
4 diseases, and that it was not necessary to kill the bacteria
5 that are normally present in the sebaceous gland in order to
6 improve acne in rosacea by prescribing these antibiotics.

7 Q. All right. Take a look, please --

8 MR. FLATTMANN: Your Honor, I have to maintain
9 my objection from this morning. The prior slide said that
10 the asserted claims were anticipated or obvious in light of
11 prior art. The very first slide they put up shows the
12 Plewig and Braun-Falco references which are not on the 282
13 notice, so I maintain the objection with the references and
14 the other six that are going to come up. Should I identify
15 those for the record so I don't have to interrupt, your
16 Honor?

17 THE COURT: Yes, that would be a good idea. Go
18 ahead.

19 MR. FLATTMANN: In addition to the DTX-1436,
20 Braun-Falco; DTX-1484, Cotterill; DTX-1493, Cunliffe;
21 DTX-1838, Plewig and Shauf; DTX-1840, Plewig; DTX-1894,
22 Smith and Mortimer; DTX-2059, Webster, and DTX-2183, Golub.
23 We maintain our objection as to those references being used
24 as prior art. Otherwise, we do not object.

25 THE COURT: The record will note your objection.

Gilchrest - direct

1 My ruling stands.

2 You may continue, Mr. Steuer.

3 MR. FLATTMANN: Thank you, your Honor.

4 MR. STEUER: Thank you, Your Honor.

5 BY MR. STEUER:

6 Q. Dr. Gilchrest, could you please turn to DTX-1840?

7 A. Yes. This is the article by, the chapter by Plewig
8 entitled, Acne, Morphogenesis and Treatment.

9 MR. STEUER: I move the admission of Defendant's
10 Trial Exhibit 1840.

11 MR. FLATTMANN: No objection with that
12 reservation, your Honor.

13 THE COURT: And with that reservation, the
14 document is admitted.

15 (DTX-1840 received into evidence.)

16 BY MR. STEUER:

17 Q. All right. Could you take a look at Defendant's
18 Trial Exhibit 1436, Dr. Gilchrest?

19 A. This?

20 Q. Yes. 1436.

21 A. I'm sorry. Yes. This is the Braun-Falco and Plewig
22 reference. Yes.

23 Q. Is this an article you cited in your expert report?

24 A. Yes, it is.

25 MR. STEUER: Your Honor, I move the admission of

Gilchrest - direct

1 Defendant's Trial Exhibit 1436.

2 MR. FLATTMANN: No objection with the same
3 reservation, your Honor.

4 THE COURT: Same ruling. It's admitted.

5 (DTX-1436 received into evidence.)

6 MR. STEUER: All right. Let's go to this slide
7 here.

8 BY MR. STEUER:

9 Q. Can you tell us what the significance is of these two
10 articles to your opinion?

11 A. Yes. Both of these articles are authored by people
12 considered very expert in the field at that time. And the
13 Plewig chapter specifically notes that it is not necessary
14 to kill bacteria acne to have a good therapeutic effect with
15 low dose antibiotics.

16 So this is something that was widely read and
17 accepted by dermatologists at that time.

18 The second article, the Braun-Falco, diseases of
19 sebaceous follicles, he notes that the mode of action of
20 tetracyclines in rosacea has not been completely
21 established. This is an investigation at the time. But it
22 was his opinion that it was not a bacterial disease and
23 that tetracyclines possess an antiinflammatory action not
24 related to the antibacterial one, therefore, acted not as
25 antibiotics in treatment of the disease.

Gilchrest - direct

1 Q. Do you have an opinion as to whether these two
2 concepts that acne and rosacea were not infectious, it was
3 not necessary to kill bacteria to treat acne and rosacea was
4 known to one of ordinary skill in the art prior to April of
5 2001?

6 A. It is my opinion it would be known. And with regard
7 to the 1975 reference, I was in training at that time and
8 that was what I was taught at that time in my training
9 program.

10 Q. All right. Let me ask you to turn to Defendant's
11 Exhibit 1838.

12 A. Yes. This is the --

13 Q. Do you recognize this?

14 A. The Journal of Investigative Dermatology, yes, study
15 by Plewig. Yes.

16 Q. Actually, this is the journal in which you will be
17 the editor-in-chief?

18 A. Yes, that's correct.

19 MR. STEUER: Your Honor, I would move
20 Defendant's Trial Exhibit 1838 into evidence.

21 MR. FLATTMANN: No objection with the previously
22 stated reservation.

23 THE COURT: It's admitted.

24 (DTX-1838 received into evidence.)

25 MR. STEUER: All right. Let's go to DDX-239.

Gilchrest - direct

1 BY MR. STEUER:

2 Q. What does Plewig tell us in this article?

3 A. Yes. This was an interesting article in which
4 Dr. Plewig used a sterile solution of potassium chloride in
5 order to induce inflammatory papules and pustules in the
6 skin of volunteers, and he noted that treatment with low
7 dose tetracyclines varied substantially the lesion count in
8 these volunteers and, therefore, must have been acting
9 through a mechanism other than killing bacteria because
10 bacteria had nothing to do with the appearance of these
11 papules and pustules.

12 Q. In your opinion, did this confirm what was known to
13 persons of ordinary skill in the art as of April 2001?

14 A. Yes. I think it was a very elegant demonstration
15 that antibacterial doses of tetracycline were not required
16 or antibacterial activity of tetracycline is not required in
17 order to improve papules and pustules in the skin.

18 Q. Dr. Gilchrest, let me ask you to turn to Defendant's
19 Trial Exhibit 1897.

20 Do you recognize this reference?

21 A. Yes. This is a paper from 1967, I believe by Smith
22 and Mortimer.

23 MR. STEUER: Your Honor, I move the admission of
24 Defendant's Exhibit 1897.

25 MR. FLATTMANN: No objection to the admission of

Gilchrest - direct

1 the exhibit with the same reservation, your Honor.

2 THE COURT: It's admitted.

3 (DTX-1897 received into evidence.)

4 BY MR. STEUER:

5 Q. Let me just quickly ask you to look at Defendant's
6 Exhibit 1493.

7 A. Yes. This is an article authored by Cunliffe in
8 1973.

9 Q. And is this a reference that you used in your expert
10 report?

11 A. Yes. Yes, it is.

12 MR. STEUER: Your Honor, I move the admission of
13 Defendant's Trial Exhibit 1493.

14 MR. FLATTMANN: Same reservation. Otherwise, no
15 objection.

16 THE COURT: It is admitted.

17 (DTX-1493 received into evidence.)

18 MR. STEUER: Let's go to the next slide, 240.

19 BY MR. STEUER:

20 Q. And what do you discuss here, Dr. Gilchrest?

21 MR. FLATTMANN: Your Honor, we object. If she
22 testifies consistent with the slide, it will be outside the
23 scope of her expert report.

24 THE COURT: The objection is noted.

25 MR. FLATTMANN: Thank you.

Gilchrest - direct

1 THE COURT: You can answer.

2 THE WITNESS: Yes. Thank you.

3 As shown in this slide, the study by Smith and
4 Mortimer showed low dose tetracycline treatment did not
5 inhibit bacterial growth in sebaceous glands in patients
6 they studied.

7 In this experiment, they recruited patients with
8 acne and treated them for periods of up to two and-a-half
9 years with varying doses of tetracycline, but the majority
10 of the patients actually received 250 milligrams daily of
11 tetracycline. And they examined patients over this period
12 of time and found improvement of acne lesions.

13 During the course of the study, they repeatedly
14 cultured pustules that were still present and showed no
15 change in the bacterial flora present in those sebaceous
16 gland of the skin, the site of origin of the acne lesions
17 and they, therefore, concluded that acne could be improved
18 or was improved with doses of tetracycline that had no
19 affect on bacterial microflora in the skin.

20 Q. In any particular part of the skin?

21 A. In the pilo sebaceous glands they cultured for
22 various periods, but up to two and-a-half years.

23 MR. STEUER: Let's go to the next slide.

24 Defendant's Demonstration Exhibit 241.

25 MR. FLATTMANN: Your Honor, we object to the use

Gilchrest - direct

1 of this exhibit. The expected testimony is outside the
2 scope of the expert report.

3 THE COURT: The objection is noted.

4 THE WITNESS: Yes. This is the study performed
5 by Cunliffe and his colleagues.

6 They recruited patients with inflammatory acne
7 and treated them with 250 milligrams daily for a period of
8 three months.

9 On the left, we see a scoring system showing
10 improvement in the inflammatory lesions of acne in these
11 patients over the three months that was statistically
12 significant. And on the right side are the results of
13 cultures obtained before and at monthly intervals during
14 treatment with this low dose of tetracycline showing no
15 reduction in skin microflora as retrieved from the pilo
16 sebaceous glands in these patients.

17 They concluded that the acne lesions in these
18 patients improved in the absence of any bacterial growth
19 inhibition as determined by repeated cultures retained from
20 pilo sebaceous glands in the skin.

21 BY MR. STEUER:

22 Q. Are these Smith and Mortimer and Cunliffe articles
23 consistent with what was known to persons of ordinary skill
24 in the art as of April of 2000?

25 A. Yes. I would say yes, in my opinion, it was in these

Gilchrest - direct

1 papers by these very well regarded authors were known to one
2 of skill in the art at that time.

3 Q. Now, you might have heard in the opening, in his
4 opening remarks, Mr. Flattmann commented that these are so
5 old. If this is so well known and such a part of common
6 knowledge, why are these references so old? Do you have an
7 opinion on that?

8 A. Yes. In my opinion, in the 1970s, and perhaps into
9 the 80s, there was disagreement in the dermatology community
10 about the role of bacteria in acne and rosacea and the
11 importance of the antibacterial effects of tetracycline
12 antibiotics in improving the disease.

13 These references in my training and in my
14 teaching were very influential in convincing the dermatology
15 community at large that it was not the antibacterial effects
16 of these antibiotics that were having the therapeutic effect
17 on inflammatory lesions of acne and rosacea.

18 Q. Now, let me ask you to look at Defendant's Trial
19 Exhibit 1764.

20 Can you identify this article?

21 A. This is the oxytetracycline treatment of acne study
22 done by John Murphy in 1962. The Murphy article.

23 MR. STEUER: Your Honor, I offer Defendant's
24 Trial Exhibit 1764.

25 MR. FLATTMANN: No objection, your Honor.

Gilchrest - direct

1 THE COURT: It is admitted.

2 (DTX-1764 received into evidence.)

3 BY MR. STEUER:

4 Q. What does Murphy disclose, Dr. Gilchrest?

5 A. Yes. I think we have a demonstrative slide. Yes.

6 Thank you.

7 Q. DDX-242.

8 A. Yes. Murphy treated 85 patients in a placebo
9 controlled clinical study. He selected patients with
10 moderate to severe acne who had inflammatory lesions, and he
11 administered 125 milligrams of oxytetracycline for six to
12 12 months and noted, as shown in the table below that while
13 the patients were being administered oxytetracycline, they
14 improved and rated -- the results were rated as excellent or
15 good in the great majority of patients, whereas when they
16 were treated with the placebo regimen, very few had such
17 good results.

18 So this was an improvement with this low dose of
19 oxytetracycline over a period of six to 12 months.

20 Q. In your opinion, does Murphy anticipate any of the
21 claims of the Ashley patents?

22 A. It does.

23 Q. And have you created a chart illustrating that?

24 A. Yes.

25 Q. Can we go to 243?

Gilchrest - direct

1 A. Right.

2 Q. Would you walk us through this, doctor?

3 A. Yes. Thank you. Thank you. It is my opinion that
4 claims 1, 22, 23, 26 and 28 of the '267 patent are
5 anticipated by this Murphy paper.

6 Q. And is this the one where counsel screwed up on the
7 heading?

8 A. Yes. Actually, I believe claim 23 should not be
9 listed as anticipated because actually the dose of
10 oxytetracycline used in this study fell below the 40 to
11 70 percent of an effective antibacterial dose that is
12 specified in claim 23. So this does not anticipate claim
13 23, only that it is an even lower dose than specified in the
14 claim language.

15 Q. All right. And the heading should have had 30?

16 A. 30, right.

17 Q. Okay. With that, please go ahead, Dr. Gilchrest.

18 A. Thank you. As highlighted here in yellow, this is a
19 method -- the claim in the patent is a method of treating
20 acne in humans -- and that is exactly what Murphy did -- in
21 a sub-antibacterial amount that reduces lesion count.

22 And Murphy administered 125 milligrams of
23 oxytetracycline, that is equivalent to 125 milligrams of
24 tetracycline, which is a sub-antibacterial amount and which,
25 as shown in the studies we just described, was not

Gilchrest - direct

1 sufficient to alter the skin microflora and pilo sebaceous
2 glands of the skin for periods of up to three months in the
3 Cotterill study or up to two and-a-half years in the
4 Mortimer study.

5 Q. All right. And why don't you take us through the
6 last three elements of the claim 1?

7 A. Yes, it was administered orally. It was, said amount
8 was 10 to 80 percent of the antibacterial effective amount,
9 in the 125 milligrams of oxy 10 is 12 1/2 percent of the
10 1,000 milligrams per day specified in the Ashley patent as
11 an antibacterial effective amount.

12 And it was administered long term, which is
13 agreed upon by the parties as more than eight to ten days.
14 And this was for many months.

15 And without administering a bisphosphonate
16 compound.

17 Q. All right. And what are your --

18 THE COURT: Hold on.

19 Mr. Flattmann.

20 MR. FLATTMANN: I'll object to this line of
21 questioning as outside the scope of her expert report to the
22 extent it purports to combine the teachings of Murphy,
23 Cotterill and Cunliffe. And also my prior objection applies
24 concerning 282.

25 THE COURT: The objection is noted.

Gilchrest - direct

1 Mr. Steuer, do you have much more on Murphy?

2 MR. STEUER: Not too much.

3 THE COURT: Okay. When are you done with
4 Murphy, we'll take our morning break.

5 BY MR. STEUER:

6 Q. Okay. Do you believe any dependent claims of the
7 '267 patent are also anticipated by Murphy?

8 A. Yes. As listed at the bottom of the slide, claim 22
9 speaks to treating moderate to severe acne patients. Claim
10 26 -- no, I'm sorry. If I could have the wording of the
11 dependent claims.

12 MR. STEUER: Can you put up claim 26 from the
13 patent?

14 THE WITNESS: No?

15 MR. STEUER: I believe it's also in your book.

16 THE WITNESS: Yes. Here we go. Okay.

17 So claim 22 is a method according to claim 1,
18 wherein we're speaking about acne rosacea.

19 So claim 23, where we already discussed it
20 should not be included.

21 Claim 26, a method according to claim 24, which
22 is skin lesions associated with acne or papules and pustules
23 which were the case in this study. And,

24 28, an antibacterial amount that results in no
25 reduction in skin microflora during the six month treatment

Gilchrest - direct

1 as we have already discussed. And,

2 Claim 30, a method according to claim 26,
3 wherein the antibacterial amount results in no reduction in
4 skin microflora during the six month treatment.

5 Again, a condition inherently met by this study.

6 MR. STEUER: Okay. Thank you, your Honor.

7 Perhaps we could break now.

8 THE COURT: Okay. We'll take our morning
9 recess.

10 (Brief recess taken.)

11 THE COURT: You may continue with your exam.

12 BY MR. STEUER:

13 Q. Hello again, Dr. Gilchrest.

14 A. Hello.

15 Q. Do you have any opinion as to whether the other
16 claims that you did not discuss regarding Murphy are obvious
17 in light of Murphy?

18 A. The others listed in the slide? It was my opinion
19 that all of those asserted claims were rendered obvious by
20 the Murphy reference.

21 Q. In the interest of time, why don't we just move ahead
22 to your third opinion. It's 250.

23 A. Yes, it is my opinion that the asserted claims of the
24 Ashley patents are obvious in view of the prior art low dose
25 tetracycline use in rosacea as well as the experience with

Gilchrest - direct

1 Periostat.

2 Q. How did you reach this conclusion, Dr. Gilchrest?

3 A. By review of the literature. I think we have a slide
4 that summarizes.

5 Q. All right. Let me ask you to turn to Defendant's
6 Trial Exhibit 1901.

7 A. Yes.

8 Q. And what is this?

9 A. Yes. This is a clinical trial of tetracycline and
10 rosacea by Sneddon.

11 MR. STEUER: I offer Defendant's Trial
12 Exhibit 1901.

13 MR. FLATTMANN: No objection.

14 THE COURT: It is admitted.

15 (DTX-1901 received into evidence.)

16 BY MR. STEUER:

17 Q. Let me ask you to take a look at Defendant's Trial
18 Exhibit 1703.

19 A. Sorry. Yes. This is the tetracycline and the
20 treatment of ocular rosacea by Marmion.

21 MR. STEUER: We offer Defendant's Trial
22 Exhibit 1703.

23 MR. FLATTMANN: No objection.

24 THE COURT: It's admitted.

25 (DTX-1703 received into evidence.)

Gilchrest - direct

1 BY MR. STEUER:

2 Q. Let me ask you to turn to Defendant's Trial
3 Exhibit 2067.

4 A. And this is long term treatment of rosacea with oral
5 tetracycline by Wereide.

6 MR. STEUER: I offer Defendant's Trial
7 Exhibit 2067.

8 MR. FLATTMANN: No objection.

9 THE COURT: It's admitted.

10 (DTX-2067 received into evidence.)

11 BY MR. STEUER:

12 Q. And let me ask you to look at Defendants' Trial
13 Exhibit 1418.

14 A. I'm sorry. 14?

15 Q. 18. 1418.

16 A. Yes. Oxytetracycline treatment of ocular rosacea, a
17 double blind trial by Bartholomew.

18 MR. STEUER: I offer Defendants' Trial Exhibit
19 1418.

20 MR. FLATTMANN: No objection, your Honor.

21 THE COURT: It's admitted.

22 (Defendants' Trial Exhibit No. 1418 was admitted
23 into evidence.)

24 BY MR. STEUER:

25 Q. If we could go to the next slide, could you summarize

Gilchrest - direct

1 these for us?

2 A. Yes. As shown, the first three were all published in
3 the 1960's in the Bartholomew paper, 1992. The Sneddon
4 study administered 250 milligrams of tetracycline twice
5 daily and 100 milligrams as a maintenance or controlling
6 dose once daily to treat the papules and pustules of rosacea
7 with good effect.

8 And the Marmion study administered 300
9 milligrams of oxytetracycline to treat ocular and cutaneous
10 rosacea, again with good effect.

11 Wereide, 150 milligrams to treat rosacea
12 effectively.

13 And the Bartholomew study, 500 milligrams
14 of oxytetracycline to treat ocular and cutaneous rosacea.

15 So all of these studies employed low doses,
16 certainly at least at maintenance sub-anti-bacterial doses
17 that would inherently not inhibit skin microflora based on
18 the prior art.

19 MR. FLATTMANN: I object and move to strike the
20 testimony concerning these written references disclosing
21 sub, because that's the first time it has ever appeared in
22 her testimony. It's outside the scope.

23 THE COURT: Outside the scope. The objection is
24 noted. Go ahead, Mr. Steuer.

25 BY MR. STEUER:

Gilchrest - direct

1 Q. Let me move to the next slide, Defendants'
2 Demonstrative 252.

3 Dr. Gilchrest, do you believe that these low
4 dose references render the Ashley patent claims obvious?

5 A. I do.

6 Q. And which claims do you believe are obvious in light
7 of these references?

8 A. Yes. In the '267 patent, as written here,
9 independent claim 1, 22, 23, 26, 28 and 30. That's because
10 of the low doses of the tetracycline antibiotics used. For
11 the 567, for the '572 patent, independent claims 1, 12 and
12 14. And claims 13, 20, 21 and 23 directed to doxycycline
13 monohydrate claims. And claim 15, sustained release and
14 once daily, and claims 24 and 26, sustained release once
15 daily preparations of doxycycline hydrate.

16 Q. Dr. Gilchrest, do you have an opinion with regard to
17 the remaining asserted claims of the Ashley patent?

18 A. Yes.

19 Q. What is that?

20 A. That this would, in essence, also be rendered obvious
21 with -- by the collection of prior art.

22 Q. Let's turn to your fourth opinion. And what is this?

23 A. The asserted claims of the Ashley patents are obvious
24 in view of prior art ocular rosacea references and --

25 Q. And let me ask you to -- what specific ocular

Gilchrest - direct

1 rosacea -- you're talking about Pflugfelder?

2 A. Yes. The Pflugfelder patent.

3 Q. All right. Let me ask you to turn to Defendants'
4 Trial Exhibit 1043.

5 A. Yes. 1045, I believe.

6 Q. 1045.

7 A. Pflugfelder patent.

8 Q. Okay.

9 A. Method for treating meibomian gland disease.

10 MR. STEUER: I offer 1045.

11 MR. FLATTMANN: No objection.

12 THE COURT: Admitted.

13 (DTX-1045 was admitted into evidence.)

14 BY MR. STEUER:

15 Q. Dr. Gilchrest, what's the relationship between
16 meibomian gland disease and facial rosacea?

17 A. Yes. As has already been I think very thoroughly
18 discussed earlier in these proceedings, meibomian gland
19 disease is a term used in the ophthalmological literature to
20 describe problems arising in the modified sebaceous glands
21 that exist in the eyelid and produces redness, soreness,
22 chalazion, and other problems with the eye.

23 Many authorities consider it to be ocular rosacea,
24 another identical synonymous term. Other authorities use the
25 term to describe a portion of the problems that arise in

Gilchrest - direct

1 people with ocular rosacea and distinguish certain other eye
2 problems that have a different name.

3 In dermatology, the term ocular rosacea is used
4 more commonly and it is used by dermatologists to describe
5 predominantly what is known in the ophthalmologic literature
6 as meibomian gland disease.

7 Q. Okay. And let me ask you to turn to Defendant's
8 Trial Exhibit 2059.

9 A. Yes.

10 Q. What's this?

11 A. This is a description chapter, entitled "Acne."

12 Q. And who is it by?

13 A. I'm trying to -- it doesn't -- it's not listed here.

14 Q. Is it perhaps by Dr. Webster?

15 A. Oh, yes. Yes. Excuse me. Yes. His name is not
16 predominantly here, but, yes, this is a chapter prepared by
17 Dr. Webster in 1996, I believe.

18 MR. STEUER: Your Honor, I offer Defendants'
19 Trial Exhibit 2059.

20 MR. FLATTMANN: Reserving the previous stated
21 objection, we don't have any other.

22 THE COURT: All right. It is admitted.

23 (Defendants' Trial Exhibit No. 2059 was admitted
24 into evidence.)

25 BY MR. STEUER:

Gilchrest - direct

1 Q. Do you have a slide that addresses --

2 A. Yes. Next slide, please.

3 Q. -- 2524?

4 A. Yes. So as already mentioned, meibomian gland
5 disease is a term that is often used synonymously with
6 ocular rosacea, and something which I believe was not -- has
7 not previously been emphasized in testimony here.

8 The treatment of systemic rosacea with --
9 treatment of rosacea with systemic agents, treatment of
10 that, of facial lesions of rosacea is well-known in the
11 dermatologic community to very frequently improve the eye
12 symptoms and signs that these patients have, and that is to
13 improve the condition that is called in the ophthalmologic
14 literature meibomian gland disease most commonly, and is
15 called in the ophthalmologic literature ocular rosacea.

16 So it has been repeatedly written and it's
17 well considered well-known that agents that treat one,
18 either the eye or the skin, will treat lesions of rosacea in
19 the other site.

20 Q. And let me call your attention to Defendants' Trial
21 Exhibit 1703.

22 A. Yes. Just to comment that the quote taken here at
23 the bottom of our slide is from this Webster article in
24 1996, in which Dr. Webster notes, as he did in his
25 testimony, that many patients with rosacea also have eye

Gilchrest - direct

1 lesions of rosacea in 50 or 60 percent or so, and treatment
2 of the rosacea with systemic medication usually produces
3 great improvement in these eye symptoms.

4 Q. Okay.

5 A. Well-known.

6 Q. Let's take a look at Defendants' Trial Exhibit 1703.
7 Do you recognize this?

8 A. Yes. This is a short paper written by Marmion,
9 tetracyclines and the treatment of ocular rosacea.

10 MR. STEUER: I offer 1703.

11 MR. FLATTMANN: No objection.

12 THE COURT: It's admitted.

13 DTX-1703 was admitted into evidence.)

14 BY MR. STEUER:

15 Q. Let me ask you to turn to 1418.

16 A. Yes. This is the Bartholomew reference,
17 oxytetracycline, and the treatment of ocular rosacea.

18 MR. STEUER: I offer Trial Exhibit 1418.

19 MR. FLATTMANN: No objection.

20 THE COURT: It's admitted.

21 (Trial Exhibit No. 1418 was admitted into
22 evidence.)

23 BY MR. STEUER:

24 Q. Let's look at the next slide. What do these
25 references say of use to us?

Gilchrest - direct

1 A. Yes. These articles again make the point that, as I
2 said, in Marmion, a high degree of correlation of the
3 changes occurring in the eye with skin disease and treatment
4 which is effective for the skin disorder, as suggested by
5 Sneddon in 1966, may therefore be of value in treatment of
6 the ocular condition. Namely, ocular rosacea, written in
7 1966. A quote from the Bartholomew paper that systemic
8 oxytetracycline is thus a useful and safe treatment for
9 ocular rosacea as well as for rosacea of the face based on
10 the study that this group performed.

11 Q. Now let's look at the next slide, which I think is an
12 experiment from the -- from the Pflugfelder patent.

13 A. Yes.

14 Q. Why did you prepare a demonstrative on this?

15 A. I forgot to make one comment on the previous slides,
16 and that is that it is my understanding that none of this
17 prior art was before the Patent Examiner at the time he
18 reviewed the -- the Pflugfelder application.

19 MR. FLATTMANN: I move to strike, your Honor.
20 There wasn't even a question to that effect.

21 THE COURT: Overruled.

22 BY MR. STEUER:

23 Q. And what is the significance of the highlighted
24 language here from the Pflugfelder patent on Defendants'
25 Exhibit 256?

Gilchrest - direct

1 A. Yes. It is strikingly similar to the Ashley patent
2 language, and it states that orally, tetracyclines or
3 chemically modified tetracyclines that have no antibiotic
4 effect used according to the present invention are
5 preferably orally administered at a dosage level from about
6 ten to about 100 percent, and preferably about 20 to about
7 80 percent of the normal antibiotic therapeutic dose. And
8 then at the bottom, it highlighted alternatively,
9 sub-antimicrobial dose means a dose having no significant
10 antimicrobial effect in vitro or in vivo.

11 Q. And if we could turn to the next demonstrative, does
12 this reflect your opinion as to whether any claims of the
13 Ashley patents are obvious in view of Pflugfelder?

14 A. Yes. In my opinion, the listed claims would be, from
15 the Ashley patent, would be obvious in view of Pflugfelder
16 based on the fact that one of ordinary skill in the art
17 would have known that treatments that treat ocular rosacea
18 or meibomian gland disease often also treat cutaneous
19 lesions, facial lesions of rosacea.

20 Q. And for the record, Dr. Gilchrest, could you identify
21 the claims that you believe are rendered obvious by Pflugfelder?

22 A. Yes. In the '267 patent, independent claim 1,
23 independent claims 22, 23, 26, 28 and 30; and in the '572
24 patent, independent claim 1, dependent claims 12 and 14, as
25 well as claims 13, 20, 21 and 23 directed to doxycycline

Gilchrest - direct

1 monohydrate; and claims 15, 24 and 26 directed to sustained
2 release and once daily preparations.

3 Q. Dr. Gilchrest, let's turn to your final opinion. And
4 what is that?

5 A. That there is no surprising result or long-felt need
6 for the Ashley patent claims.

7 Q. And what opinion do you have regarding this?

8 A. In my opinion, there was no surprising result, and my
9 basis for that opinion is that a low dose of doxycycline,
10 for example, 50 milligrams per day, was widely used by
11 dermatologists to treat rosacea. And it is my opinion that
12 no one would have expected to -- that decreasing this dose
13 by ten milligrams to treat rosacea would have not been
14 effective. And, indeed, I believe Dr. Feldman had the same
15 opinion at the time that he decided to treat his patient
16 with doxycycline, 40 milligrams.

17 Q. Do you believe there was a long-felt need that was
18 met by Oracea?

19 A. I do not. I heard yesterday Dr. Webster's testimony
20 that it was very difficult for him to treat his rosacea
21 patients in the summer when he could only use 50 milligrams
22 of doxycycline. That has not been my experience. I do not
23 find it has been a terrible problem to treat people with
24 50 milligrams of doxycycline.

25 Side effects, as I already mentioned, are

Gilchrest - direct

1 very infrequent in my experience and in the experience of my
2 colleagues, and it just has not been a problem.

3 Q. Okay. Thank you, Dr. Gilchrest.

4 A. Thank you.

5 MR. STEUER: One other thing, your Honor. We
6 have one other exhibit that I glossed over, that I was just
7 reminded of.

8 BY MR. STEUER:

9 Q. Can you take a look at Exhibit 1820?

10 A. The PDR. Yes.

11 Q. And is this the PDR for Periostat?

12 A. Yes, it is, from 2000, yes.

13 Q. And did you rely on this in making any of the obvious
14 opinions that you rendered regarding the products?

15 A. Yes. I believe that the Periostat description here
16 in the PDR is very -- is essentially identical to things
17 that were being done by the practicing dermatology
18 community.

19 MR. STEUER: I offer Defendants' 1820.

20 MR. FLATTMANN: No objection, your Honor.

21 THE COURT: It's admitted.

22 (Defendants' Trial Exhibit No. 1820 was admitted
23 into evidence.)

24 MR. STEUER: Now I'm done.

25 THE COURT: Cross-examination.

Gilchrest - cross

1 MR. FLATTMANN: Thank you.

2 CROSS-EXAMINATION

3 BY MR. FLATTMANN:

4 Q. Doctor, do you have any understanding as to why Mylan
5 wants to make a 40-milligram doxycycline product for the
6 treatment of rosacea?

7 A. I understand they believe it will be a successful
8 product.

9 Q. Okay. And Mylan already has a 50-milligram product
10 for the treatment of diseases; right?

11 A. Yes.

12 Q. Okay. But it's going to the time and expense of this
13 lawsuit to try to produce a 40-milligram doxycycline product
14 for the treatment of rosacea; is that right?

15 A. Yes.

16 Q. Okay. Now, you've been retained in this case as an
17 expert consultant in the field of clinical dermatology; is
18 that correct?

19 A. Correct.

20 Q. And you have published no original papers concerning
21 rosacea; right?

22 A. That is correct.

23 Q. Rosacea is not a common topic on which you speak;
24 correct?

25 A. Not a common topic, except in clinic.

Gilchrest - cross

1 Q. All right. You've never developed a drug for
2 rosacea; correct?

3 A. I have not.

4 Q. You have never tried to develop a drug for rosacea
5 either; right?

6 A. Correct.

7 Q. And you've never conducted a clinical trial involving
8 the treatment of rosacea; is that correct?

9 A. Correct.

10 Q. And you're not a pharmacologist and don't have any
11 formal training in pharmacology; is that correct?

12 A. Correct.

13 Q. I want to ask you a few questions about your views
14 concerning Dr. Feldman.

15 For the purpose of forming your opinion in
16 this case, you considered the deposition transcript of Dr.
17 Feldman?

18 A. Yes.

19 Q. Correct?

20 A. Yes.

21 Q. And you also considered his June 25th, 2010,
22 declaration?

23 A. Yes.

24 Q. And you've never met Dr. Feldman; right?

25 A. I have not.

Gilchrest - cross

1 Q. You've never spoken with him; correct?

2 A. No.

3 Q. You've never heard of him before your involvement in
4 this case; correct?

5 A. That is correct.

6 Q. You've never read anything that he has published;
7 right?

8 A. I've never read anything he has published.

9 Q. You've never heard him speak?

10 A. No.

11 Q. You know nothing about his reputation?

12 A. No.

13 Q. And aside from Dr. Feldman's declaration and his
14 deposition testimony, you're not aware of any other evidence
15 suggesting that Dr. Feldman ever personally took Periostat;
16 right?

17 A. I rely on his deposition.

18 Q. You're not aware of any other evidence, correct, that
19 he personally took Periostat?

20 A. Other than his testimony and deposition, no.

21 Q. Okay. And you had not seen any documents relating to
22 Dr. Feldman's alleged correspondence with CollaGenex or his
23 obtaining samples from CollaGenex; correct?

24 A. Correct.

25 Q. And you're not aware of whether, prior to his

Gilchrest - cross

1 involvement in this litigation, Dr. Feldman ever disclosed
2 his alleged use of Periostat to anyone; is that correct?

3 A. Correct.

4 Q. To your knowledge, prior to his involvement in this
5 litigation, Dr. Feldman did not ever publish anything
6 regarding his alleged personal use of Periostat; correct?

7 A. Not to my knowledge, no.

8 Q. And you're not aware of his use being published
9 anywhere in a journal or an abstract or a review article or
10 anything like that; right?

11 A. Correct.

12 Q. And you're not aware of him ever publicizing his use
13 of Periostat at all; right?

14 A. I'm not aware of that, at all.

15 Q. You're not aware of any instance, in fact, in which
16 Dr. Feldman's use of Periostat was publicly known; right?

17 A. Could you describe "publicly," please.

18 Q. You're not aware of any instance in which Dr.
19 Feldman's use of Periostat was publicly known; correct?

20 A. Could you define "publicly," please.

21 Q. You understood the term at your deposition; is that
22 correct?

23 A. To my -- I have no information that he spoke openly
24 about it, and if that is the meaning of publicly, then he
25 did not, to my knowledge --

Gilchrest - cross

1 Q. Okay.

2 A. -- publicly disclose this.

3 Q. Do you dispute that at your deposition, you stated
4 that you were unaware of any instance in which it was
5 publicly known?

6 A. In that sense of the term, yes. That's correct.

7 Q. And you had never heard of his use until you got
8 involved in this case; is that correct?

9 A. That's correct.

10 Q. And is it your understanding based on the discussions
11 with counsel that if an invention had been practiced prior
12 to the submission of a patent application, a patent for that
13 invention should not issue?

14 A. Yes.

15 Q. Okay. But in forming your opinion, you did not
16 consider whether Dr. Feldman's use of Periostat was publicly
17 known; right?

18 A. Right.

19 Q. Okay. You don't know anything about the severity or
20 the character of Dr. Feldman's rosacea or its tendency to
21 remit; correct?

22 A. Correct.

23 Q. You did not see in Dr. Feldman's deposition
24 transcript or his declaration any suggestion that he
25 performed any testing to determine if his own skin

Gilchrest - cross

1 microflora was reduced by Periostat; correct?

2 A. That is correct.

3 Q. And you did not see anything in Dr. Feldman's
4 deposition transcript or his declaration, any suggestion
5 that he performed any microbiological testing on himself
6 prior to treatment with Periostat; correct?

7 A. Correct.

8 Q. And you didn't see any evidence that Dr. Feldman
9 performed any microbiological testing on himself after
10 six months of treatment with Periostat; correct?

11 A. Correct.

12 Q. Okay. I'd like to ask you about DTX-2139 which
13 talked about in your direct testimony. That's the so-called
14 Feldman patient record.

15 A. Yes.

16 Q. Now, patient records that identify the patient are
17 precluded by HIPAA regulations from being publicly shared
18 without explicit permission from the patient; right?

19 A. Correct.

20 Q. Is it your understanding that under HIPAA
21 regulations, it would be improper to release this without
22 the patient permission if it still contained the name or any
23 identifying information?

24 A. Correct.

25 Q. And it would be unethical to disclose something like

Gilchrest - cross

1 that without the patient's permission?

2 A. Correct.

3 Q. To the best of your recollection, Dr. Feldman
4 testified that apart from this litigation, he never
5 disclosed the patient record to anyone; correct?

6 A. Yes.

7 Q. According to Dr. Feldman's testimony, it was in a
8 locked storage facility and not shared with others; correct?

9 A. Correct.

10 Q. And you are not aware of the patient record being
11 anywhere but in Dr. Feldman's files of those patient
12 records; right?

13 A. Correct.

14 Q. You have no information to suggest that he disclosed
15 the patient record at any point up until the litigation;
16 correct?

17 A. Correct.

18 Q. And there is nothing that substantiates him sharing
19 that information with anyone else; right?

20 A. Correct.

21 Q. And you don't have any reason to believe that
22 Dr. Feldman did disclose the record; right?

23 A. Correct.

24 Q. And you are not personally aware of any person other
25 than Dr. Feldman who reviewed the patient record at any time

Gilchrest - cross

1 prior to this litigation; right?

2 A. I'm not aware of that, no.

3 Q. All right. You are not aware of Dr. Feldman ever
4 publishing the record that you relied on in this case?

5 A. Right.

6 Q. To your knowledge, Dr. Feldman never, at any time,
7 published anything about his treatment of this patient;
8 correct?

9 A. Not that I know of.

10 Q. And you are not aware of Dr. Feldman discussing the
11 patient's treatment with any of his colleagues; correct?

12 A. I'm not.

13 Q. And it's not mentioned in Dr. Feldman's declaration
14 or his deposition transcript that he discussed this patient
15 or this patient's record with anyone else prior to the time
16 of the litigation; right?

17 A. Correct.

18 Q. And as we said earlier, Dr. Feldman's declaration and
19 his deposition transcript is the only information you have
20 on that issue; right?

21 A. Correct.

22 Q. I just want to be clear. You are not aware of any
23 instance at all in which Dr. Feldman publicly disclosed
24 the facts of this patient's case to anyone prior to this
25 litigation?

Gilchrest - cross

1 A. Correct.

2 Q. You are not personally aware of any instance in which
3 he even disclosed a de-identified version of the facts of
4 this patient's treatment to anyone; correct?

5 A. Correct.

6 Q. To your knowledge, Dr. Feldman never presented his
7 or his patient's alleged use of Periostat at a conference;
8 right?

9 A. Not to my knowledge, no.

10 Q. And you are not aware of Dr. Feldman ever attempting
11 to sell his idea of using Periostat to treat rosacea?

12 A. I don't think he thought it was his idea.

13 Q. All right. But you are not aware of any such
14 instance?

15 A. No.

16 Q. Now, you have never seen a copy of the original
17 prescription that was supposedly provided to Dr. Feldman's
18 patient; correct?

19 A. No, I have not.

20 Q. And that patient record itself is not a prescription;
21 correct?

22 A. That's correct.

23 Q. You don't know directly if Dr. Feldman's patient ever
24 filled her prescription; correct?

25 A. Not directly, no.

Gilchrest - cross

1 Q. Okay. In your opinion, you think there is an
2 indirect basis for presuming that the patient filled and
3 possibly refilled the prescription based on IMS data;
4 correct?

5 A. Correct.

6 Q. Now, in your review of the documents that were
7 provided regarding the IMS data, the patients names were not
8 provided; correct?

9 A. Correct.

10 Q. And the IMS data doesn't identify what the Periostat
11 was prescribed for; correct?

12 A. Correct.

13 Q. Let me ask you to look at DTX-2211. It might not be
14 in your book, doctor. Let me get a copy for you.

15 A. Yes, it's not here.

16 Q. I'm sorry. Let me make sure we get a copy right
17 away. Thank you very much.

18 MR. FLATTMANN: May I approach, your Honor?

19 THE COURT: You may.

20 MR. FLATTMANN: Here you are, doctor.

21 THE WITNESS: Thank you.

22 MR. FLATTMANN: Sure.

23 BY MR. FLATTMANN:

24 Q. And this is the IMS data that you relied on; right?

25 A. Yes. I can't read it at this scale in the Xerox but,

Gilchrest - cross

1 yes, I have seen this.

2 Q. And it doesn't say whether the prescription relates
3 to the same patient that Dr. Feldman says he prescribed the
4 Periostat for rosacea for; right?

5 A. That is correct.

6 Q. In fact, Dr. Feldman has testified that he doesn't
7 know whether the patient actually took the Periostat?

8 A. Correct.

9 Q. And you don't have any reason to dispute his
10 testimony; right?

11 A. No.

12 Q. And he obviously never saw her take the Periostat at
13 all; right?

14 A. Correct.

15 Q. And nothing in the documents you reviewed says that
16 the patient took the Periostat; right?

17 A. Correct.

18 Q. And I guess going even further, Dr. Feldman didn't
19 know if his patient took the Periostat twice daily and as
20 directed; correct?

21 A. Correct.

22 Q. That's always the situation when you prescribe a
23 treatment for a patient; right?

24 A. Yes.

25 Q. There are many reasons why that happens; right?

Gilchrest - cross

1 A. That patients don't take their medicine?

2 Q. Right. Right.

3 A. There are many reasons, yes.

4 Q. And, for instance, the general understanding is that
5 people can forget to take the drugs that are prescribed to
6 them; right?

7 A. That can happen.

8 Q. And people can change their mind about whether they
9 believe their problem is sufficiently severe to warrant a
10 medication; right?

11 A. I'm sure that is possible.

12 Q. And they might be busy and not have time to fill the
13 prescription?

14 A. It's possible.

15 Q. And they might lose the prescription; right?

16 A. That's possible.

17 Q. And some patients just don't even fill their
18 prescriptions, right?

19 A. Right. I think I met one in my deposition.

20 Q. I think I know who that was.

21 Let me hand up to DTX-1640, an article by Daniel
22 Hussar.

23 MR. FLATTMANN: May I approach, your Honor?

24 THE COURT: You may.

25 MR. FLATTMANN: There you are.

Gilchrest - cross

1 THE WITNESS: Thank you.

2 MR. FLATTMANN: Sure.

3 Q. Now, Dr. Gilchrest, this is an article by Hussar that
4 you cited as a reference in your expert report; correct?

5 A. Yes.

6 Q. Okay. And you did not mention it in your direct
7 testimony today, though; correct? When you talked about
8 Feldman?

9 A. I did not mention it, no.

10 Q. And it concerns patient compliance; right?

11 A. Yes.

12 Q. Okay. And if you go to the third paragraph in the
13 left-hand side, Hussar says problems associated with patient
14 noncompliance have been recognized for years. Would you
15 agree with that?

16 A. Of course, yes.

17 Q. In fact, it has been recognized, according to Hussar,
18 for thousands of years by no less than Hippocrates, the
19 father of Western medicine; right?

20 A. Yes.

21 Q. Hippocrates here in this article that you relied on
22 in your report said, "Keep watch also on the fault of
23 patients which often makes them lie about the taking of
24 things prescribed." Correct?

25 A. Yes.

Gilchrest - cross

1 Q. And I take it, you agree that remains wise guidance
2 for physicians today?

3 A. Yes.

4 Q. And if you look at page 971 of the document, which is
5 the first page, there is a column entitled types of
6 noncompliance in the right-hand side?

7 A. Yes.

8 Q. Do you see that?

9 A. Yes.

10 Q. And in that second paragraph in that section,
11 Hussar says that in a recent survey to consumers, 14 percent
12 respondents indicated that they had obtained prescriptions
13 from their physicians but did not have them filled.
14 Correct?

15 A. That is what it says, yes.

16 Q. If you go on to the next page under frequency of
17 administration, which is at the very bottom of the left
18 column and goes on to the right column, Hussar states in
19 that paragraph that an early study that evaluated the
20 influence on compliance of administration frequency of a
21 single drug over a 1 month period demonstrated that if
22 the agent was prescribed four times daily, 70 percent of
23 patients failed to take 25 to 50 percent of the prescribed
24 dose; three times daily after a meals, 60 failed to take
25 25 to 50 percent of the prescribed dose; twice daily,

Gilchrest - cross

1 30 percent failed to take 25 to 50 of the prescribed dose;
2 and once daily, 7 percent failed to take up to 20 percent of
3 the prescribed dose; right?

4 A. That is what it says yes.

5 Q. And this is an article you relied on in your expert
6 report in forming your opinions; correct?

7 A. Yes. Should I explain why there is no contradiction?

8 Q. No.

9 A. Okay.

10 Q. Your counsel can ask you any questions he likes on
11 redirect.

12 A. All right.

13 Q. Now, I want to be fair though and not create a wrong
14 impression. For purposes of forming your opinions in this
15 case, you did not assume Dr. Feldman's patient took the
16 Periostat at all; right?

17 A. That is correct.

18 Q. To the best of your recollection, there is no report
19 of the patient's response to any Periostat therapy; right?

20 A. That is correct.

21 Q. And whatever response the patient had to the
22 treatment that she supposedly received is not mentioned in
23 the documents that you have reviewed; correct?

24 A. Correct.

25 Q. And it's not recorded in the notes that Dr. Feldman

Gilchrest - cross

1 determined the patient's lesion count in the initial visit;
2 right?

3 A. Yes.

4 Q. Okay. And in your understanding, according to the
5 office note, the patient record we've been calling it, and
6 Dr. Feldman's testimony, the patient was asked to return
7 after three months but apparently didn't keep the
8 appointment; right?

9 A. Apparently not.

10 Q. And according to Dr. Feldman's testimony, he didn't
11 ask her about her rosacea in any follow-up visit?

12 A. Correct.

13 Q. All right. And there is no information provided
14 about any follow-up evaluation; right?

15 A. Correct.

16 Q. And Dr. Feldman, according to your recollection,
17 believes that he next saw the patient four years later?

18 A. Yes.

19 Q. Now, for the purpose of forming your opinions in this
20 case, you also did not assume that the patient's alleged use
21 of the Periostat effectively treated the papules and
22 pustules of her rosacea; correct?

23 A. Correct.

24 Q. And there is no comment anywhere in Dr. Feldman's
25 declaration or testimony about his patient's skin

Gilchrest - cross

1 microflora; correct?

2 A. Correct.

3 Q. Dr. Feldman testified he also didn't know if the
4 patient was on any medications at the time of the visit;
5 correct?

6 A. Correct.

7 Q. And you understand that it was Dr. Feldman's
8 testimony that he didn't know if the patient was on
9 medications like Boniva or Fosamax or any other drug
10 containing bisphosphonate?

11 A. Correct.

12 Q. And there is no information in the Feldman
13 declaration or testimony regarding whether this particular
14 patient suffered from osteoporosis, for instance?

15 A. Correct.

16 Q. And that is a condition that is often treated with
17 bisphosphonates; right?

18 A. Sometimes treated with bisphosphonates, yes.

19 Q. Okay. Now, you would also agree Dr. Feldman didn't
20 use a sustained release formulation of doxycycline; right?

21 A. Correct.

22 Q. And he didn't use a single 40-milligram dose of
23 doxycycline or a once daily dose; right?

24 A. Correct.

25 Q. And he didn't use a doxycycline hydrate or

Gilchrest - cross

1 monohydrate; right?

2 A. Correct.

3 Q. All right. Now, if one wanted to determine whether
4 Periostat actually works for rosacea, administering it to a
5 single patient certainly wouldn't meet the standard for
6 rigorous scientific proof; right?

7 A. That is correct. I don't think he was attempting to
8 prove anything, just practicing dermatology.

9 Q. Okay. And that is what controlled studies are for;
10 right?

11 A. That's correct.

12 Q. And you have no personal knowledge of any other
13 trials of Periostat for the treatment of rosacea by anyone
14 else prior to April of 2001; right?

15 A. I'm not aware of that.

16 Q. Now, as a medical doctor, you can prescribed drugs
17 outside your specialty; right?

18 A. Yes.

19 Q. And it's absolutely legal for a physician to
20 prescribe any approved medication for any indication; right?

21 A. Correct.

22 Q. And you have had an opportunity to review IMS data
23 that in your understanding shows that some dermatologists
24 and other physicians prescribed Periostat prior to April of
25 2001; right?

Gilchrest - cross

1 A. Correct.

2 Q. And that IMS data that you reviewed doesn't say what
3 the Periostat was prescribed for by those dermatologists?

4 A. Correct.

5 Q. What was the date of the alleged office visit?

6 A. February 19, 2000.

7 Q. Okay. I'd like to hand you a document that we've
8 marked as Plaintiffs' Trial Exhibit 407.

9 MR. FLATTMANN: May I approach, your Honor?

10 THE COURT: You may.

11 BY MR. FLATTMANN:

12 Q. Okay. Did you consider this document in forming your
13 opinions in this case?

14 A. Actually, I don't believe I have seen this letter.
15 At least, I haven't looked at the whole packet. I don't
16 recall seeing this letter to Dr. Wilkins or from
17 Dr. Wilkins.

18 Q. Okay. Please turn to that page, actually. It's
19 GAL0224899 in PTX-470, if you would.

20 Did you see -- that this is a letter from
21 CollaGenex to the FDA dated May 9th, 2000?

22 A. Yes.

23 Q. Do you see in the first paragraph of this letter, it
24 refers to a February 17th, 2000 telephone conversation
25 between CollaGenex and the FDA?

Gilchrest - cross

1 A. Yes.

2 Q. And do you see, in the next sentence, it states that
3 during this conversation of February 17th, 2000, the conduct
4 of a pilot study to evaluate Periostat in patients with
5 moderate acne was discussed in the context of conducting the
6 above referenced study?

7 A. I see that.

8 Q. And that was an IND; correct?

9 A. Um-hmm.

10 Q. Okay. And did you consider this document in forming
11 your opinion that the Feldman alleged prior use anticipates
12 the Ashley invention?

13 A. Again, I don't believe that I have seen this letter
14 before.

15 Q. Okay. I want to talk about the publications that you
16 rely upon in support of your claims that the Ashley patents
17 are anticipated or obvious.

18 You have been informed by counsel that
19 anticipation exists when a single reference contains each
20 and every element of the claim, right?

21 A. Correct.

22 Q. Okay. And in terms of your references that you rely
23 on, at your deposition you told me that you don't believe
24 that there is any one single reference that are stronger
25 than the other references, right?

Gilchrest - cross

1 A. Correct.

2 Q. Okay. And you recall that you submitted a
3 declaration earlier in this case in opposition to Galderma's
4 motion for a preliminary injunction?

5 A. Yes.

6 Q. And in that declaration, you relied on nine
7 references in support of your opinion of anticipation;
8 correct?

9 A. Yes.

10 Q. And those references were the Murphy, Knox,
11 Witkowski, Sneddon, Marmion, Wereide, Cotterill, Bartholomew
12 and Cunliffe references; right?

13 A. Correct.

14 Q. And you are now relying on six of those nine
15 references; namely, the Murphy, Sneddon, Marion, Wereide,
16 Cotterill and Bartholomew references; right?

17 A. Correct.

18 Q. You dropped three of them; right?

19 A. Yes. It's my understanding there was a request on
20 the part of plaintiffs that we reduce the list.

21 Q. All right. In any event, you are not relying on
22 those three anymore; right?

23 A. Correct.

24 Q. And one of the remaining six references is Murphy;
25 right?

Gilchrest - cross

1 A. Yes.

2 Q. One is Cotterill; right?

3 A. Right.

4 Q. Now, none of those nine, now six, references
5 explicitly disclose that the amount of antibiotic
6 administered failed to significantly inhibit the growth of
7 the microorganisms; correct?

8 A. Not explicitly.

9 Q. And none of them explicitly state that a
10 sub-antibacterial amount of antibiotic was used; correct?

11 A. That term is not used.

12 Q. Okay. And none of the references that you have cited
13 expressly talk about the lack of reduction of bacterial
14 count; right?

15 A. Noted, no.

16 Q. And none of those nine references, now six, include
17 any microflora studies; correct?

18 A. That is correct.

19 Q. Do you still have your demonstrative exhibits, Dr.
20 Gilchrest, that you used in the course of your direct?

21 A. I presume I do.

22 Q. Okay.

23 A. I don't -- I'm not good for all of that, but ...

24 Q. Oh, no. I mean do you still have the binder?

25 A. Oh, binder. Yes.

Gilchrest - cross

1 Q. I'm sorry.

2 A. Yes, I do.

3 Q. Could you please take a look at DDX-243, if you
4 would. We talked about this in your direct testimony.

5 A. 243.

6 Q. And this is a chart where you were explaining how
7 Murphy anticipated certain claims; correct?

8 A. That's correct.

9 Q. And it's a claim chart where you put down a claim
10 limitation and then you show where it is in the reference;
11 right?

12 A. Yes.

13 Q. And this is about the Murphy reference; right?

14 A. Correct.

15 Q. And next to the third row, the third row is, in a
16 sub-antibacterial amount that reduces lesion count; right?

17 A. Correct.

18 Q. And you say here, that Murphy administered
19 125 milligrams oxytetracycline for six to 12 months, a dose
20 that will not affect bacterial flora in sebaceous glands of
21 the skin. Do you see that?

22 A. Yes.

23 Q. Murphy contained no statement about bacterial flora
24 and sebaceous glands of the skin, did it?

25 A. That is correct.

Gilchrest - cross

1 Q. Okay.

2 A. It is improper --

3 Q. That's all I asked, doctor. Thank you.

4 And what Murphy did, according to the Murphy
5 paper, was confirm the value of broad spectrum antibiotics,
6 namely, that oxytetracycline; right?

7 A. He used that term.

8 Q. Okay. And you didn't use DDX-248, but I just had a
9 quick question about Cotterill. Cotterill doesn't disclose
10 any reduction and non-reduction in skin microflora either;
11 right?

12 A. Not explicitly, no.

13 Q. Okay. There is no statement about skin microflora in
14 there; right?

15 A. That's correct.

16 Q. It's not in any of the six references; right?

17 A. Not explicitly, no.

18 Q. All right. It doesn't say that that in any of the
19 references?

20 A. That's correct.

21 Q. And none of the six references disclose any blood
22 serum concentrations in humans; is that right?

23 A. No, I don't believe they do.

24 Q. All right. And you agree that none of the six
25 references disclose doxycycline as the tetracycline compound

Gilchrest - cross

1 to be used; right?

2 A. That's correct.

3 Q. All right. And none of the six references disclose
4 doses less than a hundred milligrams a day; is that right?

5 A. Equivalent doses or just doses below 100 milligrams?
6 They don't.

7 Q. All right. And in your view, as I understand it, by
8 definition in this litigation, all doses above 40 milligrams
9 of doxycycline are considered antibiotic doses?

10 A. I'm trying to -- that my understanding of what is an
11 antibiotic dose, I struggled in reading the Ashley patents
12 and was trying to determine what the Ashley patents were
13 saying.

14 Q. All right. But in your view by definition in this
15 litigation, all doses above 40 milligrams of doxycycline are
16 considered antibiotic doses; right?

17 A. The -- the Ashley patents appear to teach that, yes.
18 It's in that context that I was concerned about what the
19 specific dose might -- whether it was antibiotic or not,
20 sub-antibiotic.

21 Q. That's the definition that you adopted in this
22 litigation?

23 A. That's right. I did adopt it.

24 Q. You adopted it at your deposition; right?

25 A. Yes. Yes. I'm using that definition, yes.

Gilchrest - cross

1 Q. You're not changing that definition today?

2 A. No, I'm not.

3 Q. You've never conducted any microbiological tests to
4 determine whether 50 milligrams of doxycycline per day
5 inhibits microflora; right?

6 A. I have not.

7 Q. Okay.

8 A. I'm not aware that Ashley did either.

9 Q. You have not seen it done; is that right?

10 A. No.

11 Q. All right. And with regard to these references, even
12 though a person of skill in the art had all of these
13 references that you cite in hand since the sixties,
14 seventies and early eighties, no one developed a doxycycline
15 treatment for rosacea at any dose lower than 50 milligrams
16 per day prior to the inventors here; is that right?

17 A. I don't believe so, no.

18 Q. Okay. I'd now like to talk about Pflugfelder, if I
19 could.

20 You rely on Pflugfelder not for anticipation,
21 but for obviousness; correct?

22 A. Correct.

23 Q. Okay. And that's because Pflugfelder does not
24 address every element of the asserted claims; right?

25 A. Correct.

Gilchrest - cross

1 Q. All right. It doesn't explicitly treating a method
2 for treating the papules and pustules of rosacea; right?

3 A. No. No, it does not.

4 Q. It was considered by the Patent Examiner in
5 connection with the Ashley patent applications; correct?

6 A. Yes. He did look at the Pflugfelder patent.

7 Q. And you're aware that the Ashley patents issued over
8 Pflugfelder in the Patent Office; correct?

9 A. Yes.

10 Q. Okay. Now, certainly not all patients with rosacea
11 have been diagnosed as having meibomian gland disease;
12 right?

13 A. That's correct.

14 Q. And it's a very rare patient with rosacea who has
15 each and every sign and symptom of rosacea; correct?

16 A. As with every other disease, correct.

17 Q. All right. And characteristically, patients will
18 have some of one symptom of rosacea and very little of
19 another; right?

20 A. That's correct.

21 Q. And according to Pflugfelder, meibomian gland disease
22 occurs in approximately 50 percent of patients with the skin
23 disease rosacea; right?

24 A. Yes. And the literature says the same thing. 50,
25 60 percent or so.

Gilchrest - cross

1 Q. Okay. And in terms of the disease manifestation
2 being stated, the references that deal with the papules and
3 pustules of rosacea in your view are closer to the asserted
4 claims of the Ashley patent than Pflugfelder; right?

5 A. I am sorry. Could you repeat the question?

6 Q. Yes. In your opinion, in terms of the disease
7 manifestation at issue, the references that deal with the
8 papules and pustules of rosacea are closer to the asserted
9 claims of the Ashley patents than Pflugfelder is; right?

10 A. Can you say that in a different way? I'm not sure
11 the question you're asking.

12 Q. Sure. At your deposition, I asked you whether the
13 nine references were closer to the asserted claims than
14 Pflugfelder was, and you said that they were in terms of the
15 disease manifestation being stated.

16 Do you recall that?

17 A. Yes.

18 Q. Okay.

19 A. That they were directed, that those papers are
20 directed toward lesions that occur on the face as opposed to
21 the eyelid, yes.

22 Q. That's still your view; right?

23 A. Those particular papers, yes.

24 Q. All right. Now, you have not change or altered your
25 opinion concerning the Pflugfelder patent since the Court

Gilchrest - cross

1 rendered its preliminary injunction opinion; right?

2 A. That is correct.

3 Q. Okay. And as far as it goes with Pflugfelder, you
4 disagree with both the Patent Examiner and the Court's
5 preliminary injunction opinion; right?

6 A. I believe that the Patent Examiner, and I presume as
7 well the Court, did not have in front of them the prior art
8 references that clarified the relationship between treatment
9 responses and the disorder termed meibomian gland disease
10 and the disorder termed rosacea.

11 Q. Well, isn't it the case that with regard to
12 Pflugfelder, you disagree with both the Patent Examiner and
13 the Court on that point? That's what you told me at your
14 deposition; right?

15 A. I disagree there is no relevance -- there is no
16 obviousness concerning for Pflugfelder.

17 Q. All right.

18 A. I disagree with that.

19 Q. Okay. Now, you rely on a combination of all the
20 references that you've cited in your report to form your
21 opinion that the claims of Ashley are obvious; is that
22 right?

23 A. Yes.

24 Q. All right.

25 A. Right.

Gilchrest - cross

1 Q. And in your direct examination, you suggested that
2 the use of sub-anti-microbial doses of tetracycline would
3 have been obvious because rosacea was not believed to be a
4 bacterial disease; right?

5 A. I believe that would have been the case.

6 Q. All right.

7 A. In 2000.

8 Q. Is it fair to say that as of 2000, the cause of
9 rosacea was not fully understood?

10 A. I think it's fair to say that in 2011, it's probably
11 not fully understood.

12 Q. All right. The organism H. pylori was considered by
13 some a contributor to rosacea; correct?

14 A. By some, yes.

15 Q. And I want to take a look at one of your
16 publications, PTX-209, if we could.

17 MR. FLATTMANN: May I approach, your Honor?

18 THE COURT: You may.

19 (Mr. Flattmann handed an exhibit to the
20 witness.)

21 BY MR. FLATTMANN:

22 Q. Okay. This is one of your publications from the
23 Merck Manual of Geriatrics; correct?

24 A. Yes.

25 Q. And this was published in the year 2000; is that

Gilchrest - cross

1 correct?

2 A. Yes.

3 Q. Okay. And let's please look at page 1248 of the
4 exhibit.

5 A. The section on rosacea, yes.

6 Q. Yes. Exactly.

7 And in the first full paragraph, second
8 sentence, you state, "The etiology and path though genesis
9 are unknown, although genetic predisposition, hormonal
10 influences, psychological factors, G.I. infections or
11 demodex, folliculorum mites may play a role; correct?

12 A. That's correct.

13 Q. By this you mean at this time, in 2000, the etiology
14 and pathogenesis of rosacea were unknown; is that correct?

15 A. Yes, they were unknown.

16 Q. All right. And what does etiology mean in this
17 context?

18 A. What's causing things.

19 Q. And you thought that was a truthful statement; is
20 that correct?

21 A. Yes, I think that's a correct statement.

22 Q. And that was the state of the art in 2000; is that
23 right?

24 A. Correct.

25 Q. Okay.

Gilchrest - cross

1 A. Yes.

2 Q. Okay. Now, the references, the six references that
3 you cited are from decades before the application for the
4 claimed invention of the Ashley patents; correct?

5 A. Correct.

6 Q. And doxycycline I think you said was approved at some
7 earlier time, in the late sixties, as an antibiotic; is that
8 correct?

9 A. I don't believe I said it, but I believe that's the
10 case and it has been said.

11 Q. I apologize. I meant at your deposition.

12 A. Oh, okay.

13 Q. And I should have clarified that. But you are not
14 aware of any effort by anyone to commercialize a doxycycline
15 treatment for rosacea at any dose lower than 50 milligrams
16 per day prior to the inventors here; correct?

17 A. Right. Nobody tried to commercialize any, that is to
18 get FDA approval for any dose of any antibiotic prior to
19 Oracea.

20 Q. Specifically, you're not aware of any efforts by
21 anyone to commercialize a doxycycline treatment for rosacea
22 at any dose lower than 50 milligrams per day prior to the
23 inventors?

24 A. That is correct.

25 Q. All right. Even though the person of skill in the

Gilchrest - cross

1 art had all of these references that you cite in hand in the
2 sixties, seventies and early eighties, no one developed a
3 doxycycline treatment for rosacea at any dose lower than
4 50 milligrams prior to the inventors; is that right?

5 A. That is correct.

6 Q. All right. And based on your recollection, your best
7 guess or the first time that you used 50 milligrams of
8 doxycycline daily to treat rosacea would be in the seventies
9 or eighties; is that correct?

10 A. Yes.

11 Q. But the first time you used 40 milligrams of
12 doxycycline daily to treat rosacea was some time after
13 Oracea became available in the 2000s; correct?

14 A. That is correct.

15 Q. And you personally have never seen any other patient
16 records aside from the alleged Feldman patient record we've
17 been discussing of a doctor prescribing Periostat for
18 rosacea prior to April of 2001?

19 A. That is correct.

20 Q. And to the best of your recollection, you never
21 personally prescribed Periostat for rosacea prior to
22 April 2001; right?

23 A. Correct.

24 Q. And you've got 35 years of experience in this
25 business; right?

Gilchrest - cross

1 A. Right.

2 Q. All right. And you don't distinctly knowing anyone
3 prescribing a dose of less than 50 milligrams prior to April
4 of 2001; right?

5 A. I do not.

6 Q. All right. You're not aware of a single instance of
7 a physician prescribing Periostat for rosacea prior to April
8 of 2001 with the potential exception of Dr. Feldman; is that
9 right?

10 A. I have no knowledge of that.

11 Q. All right. And you attend a lot of conferences;
12 right?

13 A. Yes.

14 Q. And you don't recall attending any session of any
15 conference prior to April of 2001 in which a recommendation
16 was made to use Periostat to treat rosacea; right?

17 A. Correct.

18 Q. And you don't recall stating in any of your
19 publications prior to April of 2001 that you would expect 20
20 milligrams twice daily of Periostat to work for the
21 treatment of rosacea; correct?

22 A. If I had a publication before that date concerning
23 rosacea other than the one we've just discussed, I don't
24 recall it.

25 Q. All right. Well, let's take a look at one of your

Gilchrest - cross

1 publications from that time period, PTX-208. I will hand up
2 a copy.

3 MR. FLATTMANN: May I approach, your Honor?

4 THE COURT: You may.

5 (Mr. Flattmann handed an exhibit to the witness
6 and the Court.)

7 BY MR. FLATTMANN:

8 Q. Okay. Dr. Gilchrest, is this a chapter that you
9 wrote in the Geriatric Medicine, Gerontology Textbook?

10 A. Yes.

11 Q. You wrote a chapter entitled "Skin Diseases in Old
12 Age" here?

13 A. Yes.

14 Q. And this was published in 1998; is that correct?

15 A. Correct.

16 Q. If you could please turn to page 1303. In the left
17 column, you discuss rosacea; is that correct?

18 A. Correct.

19 Q. All right. And in the second paragraph, first
20 sentence of the rosacea section, you state, the acneiform
21 lesions usually respond dramatically to low dose
22 tetracycline. For example, 250 to 500 milligrams twice
23 daily, or other broad spectrum antibiotics; right?

24 A. Correct.

25 Q. So here you refer to 250 to 500 milligrams twice

Gilchrest - cross

1 daily of tetracycline as low dose tetracycline; correct?

2 A. As exemplary low doses, yes.

3 Q. And the terminology sub anti-bacterial amount does
4 not appear anywhere in your publication, PTX-208?

5 A. That's correct.

6 Q. In fact, at the time you never saw such terminology
7 being used by anyone; right?

8 A. I don't know that that is correct.

9 Q. All right.

10 A. If you look at the last sentence in the same
11 paragraph that you are highlighting, the mechanism of action
12 of these agents is unknown, but their anti-inflammatory
13 properties are suspected to play a role.

14 Q. All right. It does not say sub-anti-bacterial
15 amount, does it?

16 A. Things can be anti-inflammatory at either
17 sub-antibacterial doses or at supra antibacterial doses.

18 Q. Do you think those 250 to 500-milligram twice daily
19 doses that you recommended here were sub-antibacterial?

20 A. No, but I believe they weren't anti-inflammatory.

21 Q. They weren't sub-antibacterial?

22 A. By definition of the Ashley patents, they were not.

23 Q. And in your definition, they're not either; is that
24 correct?

25 A. There aren't a lot of infections that you want to

Gilchrest - cross

1 treat with 250 milligram twice daily.

2 Q. Well, let's look at PTX-209 again, if you have that
3 with you still. This is the chapter excerpted from the
4 Merck manual.

5 A. Mm-hmm.

6 Q. Do you still have that in front of you, doctor?

7 A. I have it here somewhere, yes.

8 Q. All right. And if you could look at the page 1248 of
9 that exhibit, you have a subject here, rosacea?

10 A. Yes.

11 Q. If you look at page 1249 under treatment -- are you
12 there? In the second paragraph, you write that mild to
13 moderate disease may be treated with topical antibiotics;
14 right?

15 A. Correct.

16 Q. And then in the next paragraph under the heading,
17 under that heading, you write, more severe inflammatory
18 disease, including eye involvement, is treated with an oral
19 antibiotic, initially at doses similar to those for acne
20 vulgaris; right?

21 A. Yes.

22 Q. And by more severe inflammatory disease, you're
23 referring to more inflammatory forms of rosacea; is that
24 right?

25 A. That's correct.

Gilchrest - cross

1 Q. And in the next sentence intended to relate to that
2 sentence suggests that what the doses were at that time and
3 are still today are often prescribed for acne?

4 A. That's correct.

5 Q. And those doses as listed here in your publication
6 are 500 milligrams twice daily of tetracycline,
7 100 milligrams twice daily of doxycycline, or 100 milligrams
8 twice daily of minocycline?

9 A. Correct.

10 Q. So specifically 100 milligrams twice daily of
11 doxycycline?

12 A. Correct.

13 Q. Those are not sub-antibiotic doses?

14 A. No, those are not.

15 Q. Okay. And in this section on rosacea, in this book
16 chapter in 2000, you don't actually describe any
17 sub-antibiotic doses for rosacea, do you?

18 A. No, but it -- just a second. It notes that response
19 is usually dramatic and that lower antibiotic doses would
20 also be effective.

21 Q. And you don't disclose any other lower doses, do you?

22 A. No, I do not.

23 Q. And this is what you wrote in 2000?

24 A. Correct. In a space-constrained manner.

25 Q. Well, you were generally trying to reflect the state

Gilchrest - cross

1 of the medical art for the various disease conditions; is
2 that right?

3 A. Yes.

4 Q. Okay.

5 A. And particularly as the most helpful to people who,
6 for example, gerontologists, who are not regularly treating
7 these diseases.

8 Q. Okay. Earlier, you discussed a 1975 reference by
9 Plewig and Kligman, DTX-1840.

10 Do you still have that in front of you, doctor?
11 I think it might be in your exhibit binder from the direct
12 examination. If not, we can provide another copy.

13 A. I'm sorry. I don't think I do.

14 Q. Let me get a copy of that for us.

15 A. I'm sorry. 1840. I'm sorry. I do have it.

16 Q. Oh, good. Okay.

17 A. I'm sorry.

18 Q. No problem.

19 A. Yes.

20 Q. Okay. And this is a reference that you discussed in
21 your direct examination?

22 A. Yes.

23 Q. And you're aware that this Plewig and Kligman
24 reference was provided to the Patent Examiner during the
25 prosecution of the Ashley patents; right?

Gilchrest - cross

1 A. Yes.

2 Q. Okay. And, in fact, it was cited by the Patent
3 Examiner?

4 A. Yes. I'd have to refresh my memory on that.

5 Q. All right. If you need to refresh your memory --

6 A. I will.

7 Q. Exhibit PTX-1.

8 A. I believe you.

9 Q. I appreciate that. Thank you.

10 Now, if we look at the Plewig reference, could
11 you please turn to Page 297? Do you see the number it lists
12 on the bottom right-hand corner? I'm just trying to orient
13 you on the page. There's a list 1, 2 down the bottom
14 right-hand corner.

15 A. Yes.

16 Q. There it is.

17 A. Yes. C. Acnes. Yes.

18 Q. And that lists is under the statement, "The facts
19 have seen to have been ascertained beyond doubt are as
20 follows"?

21 Do you see that?

22 A. Yes.

23 Q. And in the numbered list that follows is item number
24 two, do you see it states the effective drugs without
25 exception provide three measurable effects; they reduce the

Gilchrest - cross

1 population of C. acne by 95 percent or more. Do you see
2 that?

3 A. Yes. I believe I would interpret that to have to do
4 with the in vitro -- .1 in vitro assays but, yes, I see it.

5 Q. The Plewig authors believed their study established
6 beyond doubt that the effective drugs reduced the population
7 of C. acnes by 95 percent or more?

8 A. I believe that refers to the point made, .1, the in
9 vitro testing.

10 Q. And if you go to the next page, though. Item 5. The
11 very last sentence of item 5. The authors concluded that
12 all these considerations imply that it is the antibiotic
13 activity of antibiotics that accounts for therapeutic
14 benefits; correct?

15 A. Yes.

16 Q. That is something that they concluded in their view
17 beyond a doubt; correct?

18 A. That's what it says, yes.

19 Q. Okay. Now, you also mentioned the article by Plewig
20 and Shauf in your direct examination. Do you still have
21 that in front of you? It's DTX-1838.

22 A. Yes.

23 Q. Okay. And do you understand that the Plewig and
24 Shauf article was also before the Patent Office when it
25 examined the Ashley patents?

Gilchrest - cross

1 A. I believe so, yes.

2 Q. And in this Plewig and Shauf study, I think you said
3 inflammatory pustules were induced by putting potassium
4 iodide on the skin of subjects?

5 A. Potassium iodine, yes.

6 Q. And the tetracycline dose used was 1000 to
7 1500 milligrams per day; correct?

8 A. Yes. I believe so.

9 Q. That is an antibiotic dose of tetracycline?

10 A. That is correct.

11 Q. Okay. Now, let's please look at back to your slide,
12 if you would, DDX-238, which quotes some language from an
13 article by Braun and Falco. And that Braun and Falco
14 article was DTX-1436 for the record. Do you have DTX-1436
15 still in front of you?

16 A. I'm sure I do. Yes.

17 Q. Okay. And I'd like to look at the paragraph from
18 which you quote in the slide. If you turn to page 732,
19 please.

20 Could you look at the lower right-hand corner
21 under the heading "treatment?" And do you see the language
22 that you quoted in this paragraph? Namely, the mode of
23 action of tetracycline in rosacea has not been established.
24 It is not a bacterial disease. Do you see that?

25 A. Yes.

Gilchrest - cross

1 Q. Just a couple sentences above that, it states "the
2 initial dose is 1000 to 1500 milligrams divided into two to
3 three doses a day until there is significant clinical
4 improvement." Correct?

5 A. Yes.

6 Q. And that is about an antibacterial dose; correct?

7 A. Correct.

8 Q. All right. Now, would you agree the figure for the
9 number of people afflicted with rosacea in the United States
10 is something on the order of 14 million or more?

11 A. Yes.

12 Q. And as of April of 2000, in your view, was there a
13 need for improved treatment of rosacea?

14 A. There is probably still a need for improved treatment
15 for rosacea, yes.

16 Q. That need certainly existed in April of 2000;
17 correct?

18 A. Yes.

19 Q. And Oracea was the first FDA approved oral antibiotic
20 treatment for rosacea period; right?

21 A. That is correct.

22 Q. Oracea is still the only FDA approved treatment for
23 the papules and pustules of rosacea?

24 A. That is correct.

25 Q. Okay. Are there side effects associated with taking

Gilchrest - cross

1 antibiotics over a long time?

2 A. Yes.

3 Q. What are they?

4 A. There are many that vary from side effects affecting
5 the individual such as gastrointestinal upset, CNS problems,
6 photosensitivity, pseudo tumorous cerebrae (phonetic). Many
7 rare effects.

8 In addition, there is concern that long term use
9 of antibiotics broadly in the population may alter the
10 sensitivity of pathogens that could then affect either the
11 patient or other people in the population.

12 Q. So there is a concern at a public health level about
13 the development of bacterial resistance?

14 A. There is concern, yes.

15 Q. Are you aware of the drug Solodyn?

16 A. Yes.

17 Q. And it was launched around the same time as Oracea?

18 A. Yes.

19 Q. And that's a full dose antibiotic tetracycline
20 treatment, right?

21 A. It's 38 milligrams. Isn't it 38 milligrams of
22 Solodyn? What is the dose?

23 Q. I'm just going by what you told me in your
24 deposition. At your deposition, you told me that it was a
25 full dose antibiotic tetracycline, right?

Gilchrest - cross

1 A. It's a dose I think that is -- criteria of the Ashley
2 patents is a full dose.

3 Q. Okay. And you don't know why Medicis Pharmaceutical
4 Corporation would launch Solodyn, which is a full dose
5 antibiotic tetracycline treatment for acne rather than a
6 sub-antibacterial dose product; correct?

7 A. I don't know why they did it.

8 Q. Now, you agree that Oracea has been commercially
9 success; right?

10 A. Yes, I understand it is.

11 Q. And you understand that it sells well?

12 A. Yes.

13 Q. And you think it's true that most doctors try to
14 prescribe the best drug for their patients; right?

15 A. Yes.

16 Q. And, to your knowledge, your clinical judgment hasn't
17 been compromised by the marketing efforts of pharmaceutical
18 companies, including Galderma; right?

19 A. I think all physicians endeavor to make informed
20 decisions based on information and not on advertising
21 materials but based on objective evidence, and I do that
22 also.

23 Q. Okay. And you reviewed Dr. Nelson's expert report
24 about marketing in this case; right?

25 A. Yes.

Gilchrest - cross

1 Q. But you haven't conducted any independent
2 investigation into the marketing habits of Galderma; right?

3 A. I have not.

4 Q. And you don't have any information that leads you to
5 think in your experience in this industry that Galderma or
6 CollaGenex has been untruthful in its marketing about
7 Oracea; correct?

8 A. I do not.

9 Q. Okay. I just have a few more questions about some
10 of the slides that you used today, doctor. First, if you
11 could turn to slide DDX-215, please? It's in your slide
12 binder.

13 A. Okay.

14 Q. You have a chart here where you compare Ashley
15 claim 1 to Feldman's alleged use to treat his own rosacea;
16 right?

17 A. Correct.

18 Q. And the claim requires a sub-antibacterial amount
19 that reduces lesion count; correct?

20 A. Correct.

21 Q. But you don't know if Feldman counted lesions; right?

22 A. I believe he said he did not.

23 Q. Okay. Let's go to the slide, DDX-219, if you would,
24 please.

25 And this concerns your comparison of

Gilchrest - cross

1 Dr. Feldman's alleged Periostat use to treat his own rosacea
2 to claim 1 of the 572 patent; right?

3 A. Yes.

4 Q. And the highlighted term is, administered in an
5 amount that results in no reduction of skin microflora
6 during a six-month treatment; right?

7 A. Correct.

8 Q. And you saw no suggestion in his testimony,
9 Dr. Feldman's testimony that he assessed that; right?

10 A. He did not.

11 Q. All right. And let me ask you to turn, if you would,
12 to DDX-229.

13 And this is your chart showing a comparison of
14 Ashley claim 1 of the '267 patent to Dr. Feldman's
15 prescribing of Periostat to his patient allegedly; right?

16 A. Correct.

17 Q. All right. And the highlighted one here says
18 administering -- the highlighted element here says
19 administering orally or intravenously to said human in an
20 antibiotic, tetracycline; right?

21 A. Correct.

22 Q. Dr. Feldman testified she didn't know if she
23 actually took the Periostat; right?

24 A. That is correct.

25 Q. And you had no reason to dispute that, right?

Gilchrest - cross

1 A. Correct.

2 Q. And, finally, DDX-230. Almost finally.

3 You have highlighted your comparison of Ashley
4 claim 1 of the '267 to the alleged Feldman prescription use.
5 And it says, in highlight, in a sub-antibacterial amount
6 that reduces lesion count.

7 And you would agree with me Dr. Feldman didn't
8 assess whether the lesion count was reduced; right?

9 A. Correct.

10 Q. And there wasn't any information about follow-up
11 evaluation on lesion count; right?

12 A. Correct.

13 Q. If you turn to DDX-232, please.

14 You are comparing Dr. Feldman's prescription of
15 Periostat to his patient to claim 1 of the '267 patent
16 again, and you highlight, wherein the tetracycline compound
17 is administered long term; right?

18 A. Correct.

19 Q. Dr. Feldman didn't know if the patient took Periostat
20 long term in reality; right?

21 A. That is correct.

22 Q. Finally, if you go to DDX-234, you have highlighted
23 the term, administered in an amount that results in no
24 reduction of skin microflora during a six-month treatment.

25 Do you see that?

Gilchrest - redirect

1 A. Correct. Yes.

2 Q. And this involves the alleged prescription to the
3 patient; correct? Right?

4 A. Right.

5 Q. And Dr. Feldman never assessed skin microflora for
6 this patient in the six-month period and doesn't know if she
7 took it for six months or if at all; right?

8 A. That is correct.

9 Q. On DDX-235, you say that the patient record
10 anticipates dependent claims of the Ashley patent, the
11 patient record itself; right?

12 A. Yes.

13 Q. When was the patient record first published?

14 A. It was written in February 19, 2000.

15 Q. And he never disclosed the patient record to anyone;
16 right?

17 A. As far as I know, no.

18 MR. FLATTMANN: No further questions.

19 THE COURT: Okay. Thank you.

20 Any redirect?

21 MR. STEUER: A little, your Honor.

22 Can we have DDX-248 back up?

23 REDIRECT EXAMINATION

24 BY MR. STEUER:

25 Q. And this was the slide that Mr. Flattmann showed you

Gilchrest - redirect

1 during your cross; is that right, Dr. Gilchrest?

2 A. Yes.

3 Q. And does this correctly reflect your view that
4 Cotterill anticipates claim 1 of the '267 patent?

5 A. Yes.

6 Q. And is Cotterill in your binder that I gave you at
7 Exhibit 1484?

8 A. I'm sure it is. Give me just a minute.

9 Yes.

10 MR. STEUER: Your Honor, I offer Exhibit 1484.

11 THE COURT: Any objection?

12 MR. FLATTMANN: No objection, your Honor.

13 THE COURT: It's admitted.

14 (DTX-1484 received into evidence.)

15 BY MR. STEUER:

16 Q. Can you take a quick look at -- you don't even have
17 to look at it. Do you remember when Mr. Flattmann showed
18 you an article from geriatric medicine and gerontology where
19 you talked of doses of 250 to 500 milligrams twice daily of
20 tetracycline?

21 A. Yes.

22 Q. Do you treat infections with 250 milligrams of
23 tetracycline?

24 A. No.

25 Q. What is the dose in your practice of tetracycline

Chambers - direct

1 that you would use to treat a bacterial infection?

2 A. Probably 2000 grams.

3 Q. So a thousand milligrams twice a day?

4 A. (Nodding yes.)

5 MR. STEUER: Nothing further.

6 THE COURT: Thank you.

7 Doctor, you can step down.

8 You can call your next witness.

9 MR. KONG: Your Honor, Mylan calls Henry
10 Chambers.

11 THE COURT: Okay.

12 HENRY CHAMBERS, having been first duly sworn,
13 was examined and testified as follows:

14 THE COURT: Good afternoon, Dr. Chambers.

15 MR. KONG: Good afternoon, your Honor. My name
16 is Tung-On Kong. I'll be directing the examination of
17 Dr. Chambers. May I approach the witness?

18 THE COURT: You may.

19 MR. KONG: Your Honor, may I proceed?

20 THE COURT: You may.

21 DIRECT EXAMINATION

22 BY MR. KONG:

23 Q. Dr. Chambers, please introduce yourself to the Court.

24 A. I'm Henry F. Chambers, M.D.

25 Q. Dr. Chambers, what job titles do you currently hold?

Chambers - direct

1 A. I'm a Professor of Medicine at the University of
2 California San Francisco, Chief of Infectious Diseases at
3 San Francisco General Hospital and Director of the
4 Fellowship Training Program in Infectious Diseases, also at
5 UCSF.

6 Q. What educational degrees do you have?

7 A. I have a BA degree from Center college, I majored in
8 chemistry, and an MD from Vanderbilt University.

9 Q. Dr. Chambers, what board certifications have you
10 obtained?

11 A. Internal Medicine and Infectious Diseases.

12 Q. And when was your first employment as a physician?

13 A. 1977, as an intern in Medicine at UCSF.

14 Q. Dr. Chambers, what is the focus of an infectious
15 disease specialist?

16 A. The prevention, diagnosis, treatment and management
17 of infectious diseases.

18 Q. When did you receive your first academic appointment?

19 A. 1985, as an Assistant Professor at UCSF.

20 Q. As a Professor of Medicine at UCSF, what subjects do
21 you teach?

22 A. I'm in the division of infectious diseases, so my
23 teaching focuses on that. It concerns use of antibiotics,
24 antimicrobial drug resistance, diagnosis and treatment
25 infections, pharmacokinetic, pharmacodynamics, mechanisms of

Chambers - direct

1 action, epidemiology of infectious disease.

2 Q. In what types of peer-reviewed activities are you
3 engaged in?

4 A. I am Editor of Antimicrobial Agents in Chemotherapy,
5 which is the peer reviewed journal for the American Society
6 of Microbiology that publishes papers on drug resistance and
7 antimicrobial therapy and antibiotics in general.

8 I also am a peer reviewer for NIH, listed on
9 NIH study sections. I'm a peer reviewer for grant
10 applications locally at UCSF, and I review for several
11 journals including Science and New England Journal of
12 Medicine, proceeding to the National Academy of Science,
13 Clinical Infectious Disease, Journal of Infectious Disease,
14 and other publications.

15 Q. What do you do as an Editor of Antimicrobial Agents
16 in Chemotherapy?

17 A. Manuscripts that come in for publication are assigned
18 to me. I identify appropriate referees to identify those
19 manuscripts. I then review the comments and determine
20 whether the publication is acceptable for publication -- the
21 article is acceptable for publication.

22 Q. Are you regularly engaged in a research activities?

23 A. Yes, I am.

24 Q. Can you describe your research activities, please?

25 A. My research concerns bacterial pathogenesis and

Chambers - direct

1 infections. It spans from looking at various factors, to
2 clinical therapeutics, to the effects of drug resistance,
3 antimicrobial resistance, in vitro mechanisms of resistance,
4 susceptibility, and also clinical therapeutics of
5 staphylococci disease.

6 Q. Approximately, how many publications have you
7 authored that relate to the field of infectious diseases and
8 antimicrobial agents?

9 A. Approximately 200, including textbook chapters.

10 Q. Are you a member of any professional societies?

11 A. I am a fellow of the Infectious Disease Society of
12 America and American College of Physicians.

13 Q. What professional recognitions have you received?

14 A. Recently, I was awarded a Master Clinician Award,
15 which for somebody in the laboratory is a true honor. Your
16 colleagues are telling you that you are a halfway decent
17 physician -- at least.

18 Q. Dr. Chambers, how would you describe your areas of
19 specialization and expertise?

20 A. I primarily focus on therapy bacterial infections; as
21 I said, use of antibiotic agents; the pharmacology of those
22 agents, the pharmacodynamics, that determines their work,
23 why they work, their use, their misuse, and resistance to
24 susceptibility mechanisms.

25 Q. If you could, please, turn to DDX-2012 in the book in

Chambers - direct

1 front of you.

2 A. I have it.

3 Q. Could you tell me what DTX-2102 is, please?

4 A. It's a copy of my CV.

5 Q. Does DTX-2102 accurately summarize your achievements
6 and experience over the years?

7 A. Yes, it does.

8 MR. KONG: Your Honor, Mylan offers DTX-2102 for
9 admission.

10 MR. FLATTMANN: No objection.

11 THE COURT: It's admitted.

12 (DTX-2102 received into evidence.)

13 MR. KONG: And Mylan proffers Dr. Chambers as an
14 expert in the field of infectious diseases and
15 anti-microbial agents, including antibiotic resistance and
16 the pharmacokinetics and pharmacodynamics of antimicrobial
17 agents.

18 MR. FLATTMANN: No objection.

19 THE COURT: He's so recognized.

20 BY MR. KONG:

21 Q. Dr. Chambers, what question are you asked to consider
22 in connection with this case?

23 A. Whether Mylan's ANDA product has significant growth
24 inhibitory activity against bacteria.

25 Q. Dr. Chambers, did you hear the testimony of Dr.

Chambers - direct

1 Webster regarding infringement of the Ashley patents?

2 A. Yes, I did.

3 Q. Do you agree with Dr. Webster, that Mylan's ANDA
4 product contains than an amount of doxycycline that does not
5 significantly inhibit the growth of microorganisms?

6 A. No, I do not.

7 Q. I understand that you have prepared a set of slides
8 for your testimony today?

9 A. I have.

10 Q. How did you prepare those slides?

11 A. This is based on a review of several articles and
12 discussions with counsel and the preparation of the slide
13 set with the assistance of your staff.

14 Q. If we could turn to DDX-302, Dr. Chambers, what is
15 this first slide?

16 A. This is a summary of the major opinions in reference
17 to the question I was asked to discuss.

18 Q. Could you please walk us through your opinions?

19 A. Yes. First, Mylan's ANDA product does not literally
20 infringe any claim of the '267 or '572 patents. The amount
21 of doxycycline in Mylan's ANDA product will significantly
22 inhibit the growth of microorganisms. For example, bacteria
23 in a human.

24 Second, Mylan's ANDA product does not infringe
25 any claim of the '267 or '572 patents under the doctrine of

Chambers - direct

1 equivalents.

2 All of these claims require administration of an
3 amount that does not significantly inhibit the growth of
4 microorganisms. For example, bacteria in a human, whereas
5 the amount of doxycycline in Mylan's ANDA product does the
6 opposite: It significantly inhibits the growth of
7 microorganisms. Therefore, it cannot be equivalent to the
8 claimed amount.

9 Finally, the content of Mylan's label does not
10 address whether a 40-milligram daily dose of doxycycline
11 significantly inhibits the growth of microorganisms. For
12 example, bacteria in a human.

13 MR. FLATTMANN: And, your Honor, Galderma
14 objects to the testimony, elicited testimony to be elicited
15 on the second point concerning the doctrine of equivalents
16 because there's no substantive opinion on the doctrine of
17 equivalents in his report or deposition.

18 THE COURT: Your objection is beyond the scope
19 of his expert report?

20 MR. FLATTMANN: Yes.

21 THE COURT: That objection is noted. You may
22 proceed, counsel.

23 Q. Dr. Chambers, let's talk about a trays that occurs in
24 your slide there, an amount that does not significantly
25 inhibit the amount of microorganisms. What's your

Chambers - direct

1 understanding of that phrase?

2 A. That it has to have some measurable important impact,
3 either in terms of species affected or organisms within the
4 species. That it can't just be a few cells.

5 Q. Let's look at DTX-1560.

6 A. I have it.

7 Q. Dr. Chambers, can you tell us what DTX-1560 is?

8 A. I think this is part of the original patent
9 application submitted to the Patent Office.

10 Q. Dr. Chambers, did you rely on DTX-1516 when
11 formulating your opinions in this case?

12 A. Yes, I did.

13 MR. KONG: Your Honor, Mylan offers DTX-1560
14 into evidence.

15 MR. FLATTMANN: No objection.

16 THE COURT: Admitted.

17 (DTX-1560 was admitted into evidence.)

18 BY MR. KONG:

19 Q. Dr. Chambers, please turn to page GAL3800.

20 A. Yes. I see it.

21 Q. Do you see the paragraph that begins, a skilled
22 artisan?

23 A. Yes, I do.

24 Q. Did you review this paragraph in the course of
25 formulating your opinions?

Chambers - direct

1 A. I did.

2 Q. Can you tell us what this -- if this paragraph here
3 is consistent with your understanding regarding your -- the
4 phrase, does not significantly inhibit the growth of
5 microorganisms?

6 A. Yes, it does.

7 Q. And could you read for us the first couple sentences,
8 please?

9 A. A skilled artisan would have no difficulty
10 understanding the phrase substantially no antibiotic
11 activity. A few of the more sensitive bacterial cells may
12 be inhibited by a sub-antibiotic dose of a tetracycline.
13 However, a significant amount of bacteria is not inhibited
14 by a sub-antibiotic dose.

15 Q. What does it mean to you, bacterial cells there?
16 What does that mean to you?

17 A. Well, that's the individual bacterial unit, so it
18 just can't be a few of those guys. It has to be a bunch.

19 Q. Okay. Staying with the phrase, does not
20 significantly inhibit the growth of microorganisms, what
21 microorganisms are implicated by that phrase?

22 A. There is no limitation, and it refers to any
23 microorganism that is bacterial or in the human body.

24 Q. And is that -- is the phrase, does not significantly
25 inhibit the growth of microorganisms limited to any part of

Chambers - direct

1 the human body?

2 A. No, it is not.

3 Q. Before we go further, why don't we take a step back
4 and discuss microorganisms more generally and anti-microbial
5 agents as well.

6 Dr. Chambers, what is a microorganism?

7 A. Generally understood to be a single cellular life
8 form or sub-life form in the case of viruses, so it's a
9 bacterium, a virus, a yeast or a protozoan, such as the
10 malaria parasite, for example.

11 Q. And where do microorganisms live?

12 A. They live everywhere. They're on the outside of our
13 bodies. They're on each of us. They're on the desk.
14 They're on the floor. They're inside of us. They're
15 ubiquitous?

16 Q. Approximately how many bacterial cells live in or on
17 the human body?

18 A. It's estimated there are about a hundred thousand
19 billion. That's ten to the 14th.

20 Q. Ten to the 14th. And how does that compare to the
21 number of human cells we have in our body?

22 A. It outnumbers our own cellular content by a factor of
23 ten.

24 Q. So that would be ten to the 13th?

25 A. Yes.

Chambers - direct

1 Q. What effect do microorganisms have on our bodies?

2 A. They can be innocuous and merely colonize. They can,
3 of course, cause disease, that's just the way we think of
4 them, and they can also be beneficial.

5 Q. Let's talk about antibacterial agents now. What is
6 an antibacterial agent?

7 A. It's a chemical substance that in dilute amount
8 inhibits the growth of microorganisms in this case,
9 bacteria.

10 Q. And during the course of this trial, we've heard some
11 testimony regarding doxycycline. What is your experience
12 with doxycycline?

13 A. I have used it therapeutically in patients and
14 studied it in the laboratory.

15 Q. How would you describe doxycycline as an antibiotic?

16 A. It is very broad spectrum. That is, it treats a
17 number of infections and affects a large number of organisms
18 and it is very potent, among the most potent antibiotics
19 that we use.

20 Q. How does doxycycline administered to a patient?

21 A. It is administered either topically, orally, or by
22 vein.

23 Q. When administered orally, how does doxycycline find
24 its intended target?

25 A. It's absorbed in the proximal small bowel, enters the

Chambers - direct

1 bloodstream, and wherever the blood goes, it takes
2 doxycycline with it.

3 Q. And beyond its intended target, what off target
4 effects does doxycycline have?

5 A. So there are two off targets. One is the target of
6 the host. That is adverse events or side effects from
7 chemical effects of the drug, or there, of course, are off
8 targets, anti-microbial effects. So a drug directed against
9 a particular path general, as doxycycline would be, will
10 also pick off innocent by-standers if they are susceptible.

11 Q. How does doxycycline inhibit the growth of the
12 microorganism or pick them off as you reference?

13 A. It's a protein synthesis inhibitor, so it paralyzes
14 the protein machinery of the organism.

15 Q. And what happens when a microorganism's protein
16 machinery is paralyzed?

17 A. It interferes with growth and in sufficiently high
18 doses can shut it down entirely.

19 Q. How do you measure whether doxycycline has an
20 inhibitory effect in a human?

21 A. There are three ways in a human. One is to, with the
22 knowledge that it inhibits an organism in the test tube at
23 low concentrations, and then a patient who has an infection
24 caused by that organism upon administration of the drug, you
25 would note the elimination or drop in counts of that

Chambers - direct

2 Secondly, you would observe for emergence of
3 resistance. That is, the anti-microbial fact that exists in
4 the population leads to emergence of resistance of the drug
5 administered.

10 Q. Dr. Chambers, have you reviewed any in vivo studies
11 in connection with formulating your opinions in this case?

13 Q. Could you turn, please, to DDX-2097?

15 Q. What is DTX-2097?

19 Q. Did you rely on DTX-2097 for purposes of your work in
20 this case?

22 MR. KONG: Mylan offers DTX-2097 into evidence.

24 THE COURT: It is admitted.

Chambers - direct

1 BY MR. KONG:

2 Q. Dr. Chambers, if I refer to DTX-2097 as the Haffajee
3 study, would you understand what I mean?

4 A. I will.

5 Q. Did Dr. Webster discuss the Haffajee study?

6 A. No, he did not.

7 Q. Who funded the Haffajee study?

8 A. The National Institutes of Health.

9 Q. And if we look at DDX-303, Dr. Chambers, what is
10 DDX-303?

11 A. This is a summary that we prepared for describing the
12 study. It's a randomized single blind trial. Patients were
13 treated with one of the following: Scale and root planning
14 alone and then three groups included the administration of
15 various antibiotics, so SRP combined with doxycycline,
16 20 milligrams twice daily for three months, or SRP combined
17 with metronidazole, 250 milligrams thrice daily for 14 days,
18 or SRP combined with azithromycin, 500 milligrams once daily
19 for three days.

20 All patients received maintenance SRP post
21 therapy three, six and 12 months after the post-therapy
22 period. And subgingival plaque, they referred to it as
23 bio-films, and saliva samples were selected at baseline
24 prior to administration of any drug two weeks, three months,
25 six months and 12 months.

Chambers - direct

1 Q. Dr. Chambers, could you tell us what scaling and
2 group planing is?

3 A. It is a treatment to remove plaque in patients who
4 have periodontal disease.

5 Q. And the total daily dose of doxycycline used in the
6 doxycycline group was how much?

7 A. 20 milligrams twice a day.

8 Q. So if my math is correct, that's 40 milligrams daily?

9 A. Yes.

10 Q. What is azithromycin, Dr. Chambers?

11 A. Azithromycin is a macro lite antibiotic.

12 Q. How would you characterize a 500-milligram, once
13 daily doze of azithromycin for three days?

14 A. That's a therapeutic dose of that drug.

15 Q. What is metronidazole?

16 A. It's an antibiotic that's active against anaerobic
17 organism specifically.

18 Q. How would you characterize a 250 milligram dose of
19 metronidazole twice daily?

20 A. That is the therapeutic dose.

21 Q. Dr. Chambers, what is your opinion regarding the data
22 in the Haffajee study?

23 A. That recipients of doxycycline showed evidence of
24 significant inhibition of bacterial growth.

25 Q. And what data in particular do you rely upon?

Chambers - direct

1 A. The data from figure 3.

2 Q. Okay. Page 152 of the Haffajee study, is that figure
3 3, Dr. Chambers?

4 A. Yes. And in particular, the example from the
5 right-hand corner.

6 Q. Okay. Now, you said earlier that the emergence of
7 resistance was evidence of inhibition of growth here; is
8 that right?

9 A. Yes, it is.

10 Q. And if we could, let's look at DDX-305.

11 A. Okay. This demonstrative shows how growth inhibition
12 drives emergence of resistance to the administered
13 antibiotic.

14 Q. Dr. Chambers, in DDX-305, did you take this data from
15 any study?

16 A. No. This is just a hypothetical study to show how
17 the phenomenon works.

18 Q. And the phenomenon is what?

19 A. Selection of resistance by inhibition drug.

20 Q. Okay. I see there are a couple groups up there. Can
21 you explain what those groups consist of?

22 A. Yes. We have the doxycycline group on the top, and
23 then a placebo group that is every way identical other than
24 receiving doxycycline on the bottom.

25 Samples are taken at various time periods.

Chambers - direct

1 The time zero is the baseline sample prior to administration
2 of any drug.

3 Q. And I see that it's times zero. There is some
4 evidence of resistance in both groups. Why is that?

5 A. Yes. So in both groups, the resistance starts out
6 the same because there has been a selected pressure of the
7 drug. The red, although it is red for me, it's probably
8 brown for everybody else, in the little wedge there is the
9 doxycycline-resistant group in the doxycycline recipients.

10 And kind of this purple pink color in the
11 placebo group represents the proportion of resistant
12 organisms in those patients at the start of therapy.

13 Q. Can you explain why it's fair to assume that
14 resistant organisms will be present in the absence of drug
15 exposure?

16 A. If the drug has been around for awhile, then there
17 will already have been selection for resistance. It may be
18 carried in normal flora.

19 Secondly, there are some organisms that are
20 intrinsically resistant to the antibiotic on the basis of
21 that's their biology.

22 Q. Can you take us forward to time one here and describe
23 what's going on in both groups?

24 A. So after obtaining the baseline samples of times 0,
25 drug placebo is given at the top. What has happened is, you

Chambers - direct

1 can see the wedge of the drug resistant organisms has grown
2 larger. That's because the doxycycline has inhibited the
3 growth of the susceptible organisms and they're not able to
4 compete, and in that setting, the resistant organisms have
5 an advantage and grow up.

6 In the placebo group, that wedge is about
7 the same size. What has happened there is there is no
8 selective advantage, and so they're an equilibrium and not
9 under antibiotic selected pressure, so the susceptible cells
10 are able to maintain their normal growth, no inhibition of
11 growth, and their proportion remains the same.

12 Q. Moving forward to times two, what is depicted in
13 those two circles?

14 A. This is just meant to illustrate the continued
15 selection pressure for resistance, and now you can see the
16 wedge has now taken up of our circle as the susceptible
17 organisms consider to be out-competed due to the inhibition
18 of their growth.

19 And down below in the placebo group, you
20 can see the wedge is a little larger there. What that is
21 meant to depict is the natural variability that occurs in
22 populations of resistance. They don't have anything to do
23 with selective pressure. But if you compare the two at time
24 one and time two, there's no doubt in this example the
25 selective pressure of doxycycline by inhibiting successful

Chambers - direct

1 organisms.

2 Q. Doctor, if you could slow down your pace of speech, I
3 see smoke coming out of the Court Reporter's ears.

4 A. Slow it down.

5 Q. So understanding that this is a hypothetical, what
6 conclusions would you draw from the relative differences
7 between the groups seen at time one and time two?

8 A. Doxycycline significantly inhibited the growth of the
9 susceptible population of organisms leading to over growth
10 of the resistant population.

11 Q. Okay. So let's step out of the hypothetical now and
12 step back into the Haffajee study. If we could turn to
13 DDX-304.

14 Dr. Chambers, could you tell us what's depicted
15 here in DDX-304?

16 A. Yes. This is one of the panels from figure 3 of
17 Haffajee, looking at the effect of doxycycline
18 administration on emergence of drug resistance.

19 Q. And if we could, why don't we walk through this
20 graph.

21 What do the numbers on the X axis represent?

22 A. So the X axis shows the time period under which the
23 study was conducted and each of the numbers is when a sample
24 was taken. So at zero, the two weeks, three months,
25 six months, and 12 months.

Chambers - direct

1 Q. And then on the Y axis, what do those numbers
2 represent?

3 A. That shows out of the organisms that were covered
4 what percent were able to grow in the presence of 24
5 micrograms per million of doxycycline, which they used to
6 find resistance.

7 Q. And the red dots and pink dots with testing and
8 control next to them, what do they refer to?

9 A. Well, the test, which is kind of brownish there,
10 is -- it depicts the samples from the recipients who were
11 administered doxycycline, and the not very pink/pink are
12 samples from subjects who were in the SRP group only.

13 Q. Okay. And then on the graph there, I see a gray
14 shaded area. What does that gray shaded area refer to?

15 A. That's the period of time over which the doxycycline
16 was administered.

17 Q. Okay. So now let's talk about the data that's
18 reflected here.

19 At time zero, what percentage of resistance
20 isolates are found within the doxycycline group and the SRP
21 only group?

22 A. You can see it's close to zero. In fact, it would
23 translate to about ten percent in both groups.

24 Q. I'm going to point out screen right here now. Are
25 you referring to these two dots down here?

Chambers - direct

1 A. Yes, I am.

2 Q. Okay.

3 A. They're superimposed pretty much.

4 Q. And at the two-week time point, what percentage of
5 resistant isolates are found within the respective groups?

6 A. So in the SRP group only, it's about the same as
7 baseline, approximately ten percent, but in the doxycycline
8 recipients, there has been a spike of resistance. In fact,
9 about a fourfold increase in the number of resistant
10 organisms relative to baseline, and so it's now just a bit
11 south of half the organisms are resistant.

12 Q. In your opinion, why are the two values at the
13 two-week period different?

14 A. Because of inhibition of susceptible organisms and
15 the selection of resistant cells.

16 Q. Is there any other explanation for that?

17 A. No.

18 Q. I see above the red dot at the two-week period, it
19 says that P is less than 0.001.

20 Do you see that?

21 A. Yes. That's a statement of the likelihood that this
22 result is due to chance alone. And what that says is it's
23 not very likely. It's less than one in a thousand would you
24 get this result by chance alone.

25 Q. Okay. And, Dr. Chambers, could you walk us through

Chambers - direct

1 the next few sampling periods of three, six and 12-month
2 periods?

3 A. Yes. So at the three-month period, you see the graph
4 shows dots that are about the same, so there's no additional
5 outgrowth of resistant population. The portion remains the
6 same. It is still highly significantly different from the
7 control group.

8 And then withdrawal of the antibiotic, you see
9 the selected pressure and disadvantage of growth and lack of
10 growth inhibition of central populations. They start to
11 catch up. So you see it drop off and the number of
12 resistant organisms such that by 12 months, there's no
13 significant difference between the tests and the control and
14 it's basically headed back to baseline.

15 Q. So what, if any, long term effect of doxycycline is
16 demonstrated by this data?

17 A. Well, this shows the effects of the sustained
18 population during the period of drug exposure, and then once
19 that selected pressure is removed, it regresses back to the
20 baseline so there's no long-term pressure.

21 Q. Slow down.

22 A. Slow down.

23 Q. In terms of --

24 A. I'm trying to get my lecture done.

25 Q. In terms of infringement of the Ashley patents, how

Chambers - direct

1 does the data illustrated in figure 3 of the Haffajee study
2 form your opinion?

3 A. Well, the infringement claim would require that,
4 administration of this dose of doxycycline would not inhibit
5 microorganisms; and what this shows is significant growth
6 inhibition in a human with administration of that dose of
7 doxycycline.

8 Q. Let's now turn to DDX-2121, please.

9 Dr. Chambers, what is DTX-2121?

10 A. This is a study by Thomas, et al, also looking at
11 doxycycline at 20 milligrams twice a day, and other doses as
12 well.

13 Q. Dr. Chambers, did you rely on DTX-2121 while
14 formulating your opinions in this matter?

15 A. Yes, I did.

16 MR. KONG: Mylan offers DTX-2121 into evidence.

17 MR. FLATTMANN: No objection.

18 THE COURT: It's admitted.

19 (DTX-2121 received into evidence.)

20 BY MR. KONG:

21 Q. Dr. Chambers, if I refer to DTX-2121 as the Thomas
22 study, you understand what I mean; right?

23 A. Yes.

24 Q. Dr. Chambers, did Dr. Webster discuss the Thomas
25 study during his testimony?

Chambers - direct

1 A. No, he did not.

2 Q. Let's go to DDX-306.

3 Dr. Chambers, what appears here on DDX-306?

4 A. Again, this is a summary of a study conditions for
5 Thomas, 2000.

6 Q. Can you walk us through it, please?

7 A. Yes. It's a randomized double-blind placebo
8 controlled trial in patients with periodontitis. Patients
9 received one of four treatments. Doxycycline 20 milligrams
10 twice a day. Half that dose of doxycycline, 20 milligrams
11 once a day. Half again that dose, 10 milligrams once a day.
12 And then placebo.

13 All the patients received supragingival
14 prophylaxis at the time points of 0, 6, 12, and 15 to
15 18 months, and then subgingival plaque samples were
16 collected at zero, 12, towards the end of study, exit, 15 to
17 18, and then after a washout period of a few months at 21 to
18 24 months, off therapy.

19 Q. Dr. Chambers, what data in the Thomas study forms
20 your opinion regarding significant inhibition of growth?

21 A. It showing significant inhibition of growth in both
22 the 20 milligram twice daily group and in the 20 milligram
23 once daily group.

24 Q. What data in particular within the Thomas study do
25 you rely upon for your conclusion?

Chambers - direct

1 A. It's figure 2.

2 MR. KONG: Okay. Let's turn to DDX-307.

3 BY MR. KONG:

4 Q. Dr. Chambers, what is depicted here on DDX-307?

5 A. This shows the MIC 50 values for one of the two
6 target organisms that they elected to follow. This is for
7 actinomyces species isolates, the MIC 50 value. It's a
8 median value. It is the number of the average MIC. It's
9 represented by half of the organisms that were in the sample
10 collection.

11 Q. What do MIC 50 values tell you with respect to
12 significant inhibition of growth?

13 A. If there is an increase in the MIC 50 value in the
14 presence of antibiotic, that would indicate emergence of
15 resistance because half the organisms are able to survive a
16 much higher MIC than they started out with.

17 Q. So please tell us what the baseline values for the
18 four various groups appear to be.

19 A. Okay. In the X axis, we have the sampling period,
20 and in the baseline period, you see the little four bars
21 there, one hardly but it is there, of what the MIC 50 was
22 for isolates prior to exposure to drug or placebo.

23 Q. And what is reflected by the data at 12 months?

24 A. You can see for the 20 milligram once daily dose in
25 the kind of yellow green, and then the white box, the

Chambers - direct

1 20milligram twice daily dose, whereas the baseline MICs in
2 these organisms were 1, it is now 32 micrograms per mil, so
3 several fold increase.

4 Q. How do you explain the difference between the
5 baseline and the 12 month data for the 20 milligram
6 twice-a-day and 20 milligram once-a-day groups?

7 A. This is inhibition of strains that are not able to
8 tolerate concentrations of the drug and their growth is
9 inhibited with the subsequent selection of more resistant
10 organisms.

11 Q. How does this result compare to what we saw in the
12 Haffajee study?

13 A. It is driven by the same phenomenon, it is just a
14 different yardstick. They measure resistance at 4. This
15 just shows you how much resistance there is in their
16 population.

17 Q. And please walk through the remaining data here in
18 figure 2A.

19 A. So the study exit. This is the sample of patients
20 still on drug. And you can see there is, although a bit
21 lower, they're still persistence of resistance in the 28
22 milligram once daily group, not so marked in the BID group,
23 and then upon withdrawal of the drug at six months, the MIC
24 50 is returned to baseline again and there is no evidence of
25 the prior resistance in those populations.

Chambers - direct

1 Q. So what, if any, long term effect of doxycycline is
2 demonstrated by the data in figure 2A?

3 A. There is no long term effect shown by these data.

4 Q. In terms of infringement of the Ashley patents, how
5 does the Thomas study inform your opinion?

6 A. Well, again, it shows what I have already shown with
7 the Haffajee study, that the antibiotic dose administered
8 is sufficient to inhibit the growth of organisms, and that
9 there is overgrowth of a resistant subpopulation of
10 organisms. In the prior example, almost 50 percent, and
11 this example here, about that number, too, because the MIC
12 50 is also in the resistant level.

13 Q. So let's put away the Thomas study and turn to
14 DTX-2120.

15 THE COURT: Let's save that one for after lunch.
16 We'll take about a 45 minute recess and we'll return.

17 (Luncheon recess taken.)

18 THE COURT: Good afternoon. You may continue.

19 MR. KONG: Thank you, your Honor.

20 BY MR. KONG:

21 Q. Dr. Chambers, welcome back.

22 A. Thank you.

23 Q. Would you please turn to DTX-2120 in your book,
24 please?

25 A. I have it.

Chambers - direct

1 Q. What is DTX-2120?

2 A. It's study by Walker, et al looking at the effect of
3 doxycycline on microflora of the mouth.

4 Q. Did you rely on DTX-2120 for purposes of your work in
5 this case?

6 A. Yes, I did.

7 MR. KONG: Mylan offers DTX-2120 into evidence.

8 MR. FLATTMANN: No objection.

9 THE COURT: It's admitted.

10 (DTX-2120 received into evidence.)

11 BY MR. KONG:

12 Q. If I refer DTX-2120 as the Walker 2000 study, you
13 will understand what I mean?

14 A. Yes.

15 Q. Did Dr. Webster discuss the Walker 2000 study in his
16 testimony yesterday?

17 A. No, he did not.

18 Q. Let's look at DDX-308. What is DDX-308, doctor?

19 A. This is a summary of the study design of the Walker
20 2000 study.

21 Q. Would you walk us through this please?

22 A. So this is a randomized double-blind placebo
23 controlled trial of subjects with periodontitis who receive
24 scaling and root planing but also placebo or doxycycline
25 20 milligrams twice a day, so effectively there are four

Chambers - direct

1 groups.

2 Samples of subgingival plaque were collected for
3 examination at three, six, nine and 12 months. And the
4 examination was microscopic but also some culturing.

5 Q. Were samples also collected at baseline?

6 A. Yes. I'm sorry. I missed that.

7 Q. If we could turn to page 1467 in the Walker 2000
8 study.

9 You see tables 1 and 2 on 1467, Dr. Chambers?

10 A. I do.

11 Q. And then also on page 1468, there is a table 3 there.
12 Do you see that?

13 A. Yes, I do.

14 Q. What do these data show?

15 A. These data show significant inhibition of growth of
16 bacteria in the doxycycline group. In this case,
17 spirochetes. There are three sizes morphologically
18 distinguished. These organisms are difficult or not
19 possible to grow so they had to count them and enumerate
20 them under the microscope and the data to show what happens
21 over time in terms of this population of organisms in the
22 two groups.

23 Q. Dr. Chambers, what is a spirochete?

24 A. Spirochete is a gram negative spiral bacillus.

25 Q. Is that a type of microorganism?

Chambers - direct

1 A. It is a type. It is a bacteria.

2 Q. Let's now turn to DDX-309, please.

3 Dr. Chambers, what is DDX-309?

4 A. These are data taken from figure 1, comparing the SRP
5 parameters or the SRP therapy with and without doxycycline
6 and placebo.

7 Q. So would I understand correctly this data is taken
8 from table 1 of the Walker 2000 study?

9 A. Yes.

10 Q. And what is mean percentage of small spirochetes?
11 What does that mean?

12 A. So what they did was enumerate this morphotype by
13 looking under the microscope, and then they count all the
14 organisms, and this is a display of the percentage of this
15 group of organisms from all those that were observed.

16 Q. And let's walk through the data, Dr. Chambers,
17 starting at time zero, please. What is the relative mean
18 percentage of small spirochetes in each of the groups
19 represented in this graph?

20 A. So, here they're practically superimposable and at
21 baseline, that is zero, about 10 percent of the organisms
22 are spirochetes.

23 Q. And before we go any further, the SRP plus doxy, that
24 legend again on the upper right, what is that?

25 A. That is samples from patients that received that

Chambers - direct

1 therapy, and that's indicated by the blue diamond and then
2 in the pink boxes are the placebo recipients.

3 Q. Okay. So how does the data differ between the zero
4 and three month time points?

5 A. So as you can see over the treatment phase, with
6 initiation of doxycycline, there is a significant reduction
7 indicated by a P value of 0.05 in the number of spirochetes
8 compared to placebo recipients.

9 Q. And what does a P value of less than 0.05 indicate?

10 A. That means the chance that that difference by chance
11 alone is on the order of 1 in 20 or less than five percent.
12 Less than or equal to five percent.

13 Q. What is your interpretation of the data at the three
14 month time period?

15 A. This shows a significant growth inhibition of this
16 group of organisms, small spirochetes, due to doxycycline
17 inhibition and exposure.

18 Q. Could you walk us through the remaining time points
19 in this slide, please?

20 A. So you can see at six months, the result is not that
21 much changed. There has been a little change, practically
22 none in the placebo group in pink, but the doxycycline
23 recipients still have suppression of this population.

24 Up to nine months, the physical means are
25 beginning to alter the flora. You can see there is a drop

Chambers - direct

1 off to about six percent at the end of treatment with the
2 SRP itself. And the doxycycline group has remained stable.
3 So those are no longer different but different from
4 baseline.

5 And then from nine to 12 months, that's the
6 washout period where the drug has been withdrawn. You can
7 see a rebound in both classes of patients, both groups of
8 patients and no significant difference between the two.

9 Q. What, if any, long term effect of doxycycline is
10 demonstrated by this data here?

11 A. They don't go out beyond 12 months, but you can see
12 that those values are returning to baseline, so there is no
13 long term effect.

14 Q. In terms of infringement of the Ashley patents, how
15 does the data illustrated in tables 1, 2, and 3 of the
16 Walker 2000 study inform your opinion?

17 A. It's another example of antibiotic inhibition of
18 bacterial growth. In this case, these organisms have been
19 diminished in terms of numbers with respect to the overall
20 population, so there has been a shift in numbers.

21 Q. Let's now turn to what has been previously admitted
22 as PTX-394.

23 A. Yes.

24 Q. What is PTX-394?

25 A. This is the Skidmore study of patients with acne who

Chambers - direct

1 received doxycycline or placebo.

2 Q. If I refer to PTX-394 as the Skidmore study, you will
3 understand what I mean?

4 A. Yes.

5 Q. Let's look at DDX-310. Dr. Chambers, what appears
6 here on DDX-310?

7 A. This is a summary of a trial design. This was
8 actually a randomized double-blind clinical trial comparing
9 doxycycline to placebo. These patients were randomized to
10 receive one of the other drugs.

11 In addition, patients underwent swab testing for
12 culture of the glabella. These samples were collected and
13 at study entry times zero, and then six months at the end of
14 the study.

15 As this was a clinical trial, I noted there was
16 one subject in the doxycycline group who discontinued
17 participation in the study due to vaginitis. That was a
18 drug related adverse event.

19 Q. What is vaginitis?

20 A. The vaginitis in this case was -- the yeast vaginitis
21 was, is an overgrowth of the yeast in the vagina due to
22 alteration of the normal bacteria flora. In this case, it
23 occurred in association with administration of doxycycline.

24 Slow it down.

25 Q. Thank you.

Chambers - direct

1 Who concluded that the vaginitis suffered by
2 this subject was due to the doxycycline treatment?

3 A. It's reported in the paper itself.

4 Q. Did you hear Dr. Webster's testimony regarding the
5 Skidmore study?

6 A. Yes, I did.

7 Q. Do you agree with Dr. Webster that the Skidmore study
8 evidences that a 40 milligram daily dose of doxycycline does
9 not significantly inhibit the growth of microorganisms?

10 A. Not entirely.

11 Q. Not entirely?

12 A. Because I think when the patient with vaginitis, that
13 that is a side effect of the microorganisms in the vagina,
14 and that led to the yeast infection due to overgrowth.

15 The glabella swabs, though, however, I agree
16 the testing showed no evidence of shift in microflora.

17 Q. Dr. Chambers, did you hear my colleague Mr. Steuer
18 discuss a positive control during his opening statement?

19 A. Yes, I did.

20 Q. Could you tell us what a positive control is?

21 A. A positive control is a design feature that allows
22 you to exclude a negative result as being due to a false
23 negative.

24 Q. What impact does -- first of all, did the Skidmore
25 study include a positive control?

Chambers - direct

1 A. No, it did not.

2 Q. What impact does the lack of a positive control have
3 on your ability to scientifically interpret the Skidmore
4 data?

5 A. So the inability to observe an effect could be due to
6 the fact that you missed a true positive because it is a
7 false negative result because you don't know how the
8 positive control would have behaved.

9 Q. Are you able to exclude the possibility of false
10 negatives from the Skidmore study?

11 A. No, I'm not.

12 Q. Have we reviewed a study today that does have a
13 positive control?

14 A. Yes. The Haffajee study had two positive controls.

15 Q. What were those?

16 A. The hemedromydrazol (phonetic) and azithromycin.

17 Q. Let's turn to PTX-413 which has already been
18 admitted.

19 Dr. Chambers, what is PTX-413?

20 A. This is the Walker study of patients with
21 periodontitis receiving doxycycline 20 milligrams twice a
22 day.

23 Q. If I refer to PTX-413 as the Walker 2005 study, you
24 will know what I mean?

25 A. Yes, I do.

Chambers - direct

1 Q. What was the purpose of the Walker 2005 study?

2 A. It was to examine changes in intestinal, rather,
3 stool flora representing the intestinal flora and vaginal
4 flora as a consequence of exposure to doxycycline or
5 placebo.

6 Q. Let's take a look at DDX-311.

7 Dr. Chambers, what is DDX-311?

8 A. So this is a randomized double blind, again, placebo
9 controlled trial of doxycycline twice a day versus placebo.

10 The treatment, as I said, was administered for
11 periodontal disease but the sampling was obtained from stool
12 and vaginal flora at baseline that is times zero, three
13 months, and nine months into the study.

14 Q. And I see in your summary it says vaginal data
15 insufficient to analyze. Why do you say that?

16 A. The sampling of the vaginal data was not what was
17 targeted to allow meaningful statistical analysis, so it's
18 not possible to definitively conclude what the data showed.

19 Q. And how do you form that conclusion?

20 A. They discuss that in the paper itself.

21 Q. Turn to PTX-413 at page 1166, please. On the bottom
22 right-hand corner.

23 Is this the section to which you refer,

24 Dr. Chambers?

25 A. Yes. And I believe it continues a bit on the second

Chambers - direct

1 page -- next page as well.

2 Q. If you could look at the last sentence on this page,
3 please?

4 A. It says that the number of isolates obtained was too
5 few to allow any meaningful analysis in regard to the
6 particular bacterial species present.

7 Q. Do you disagree with that statement?

8 A. No, I do not.

9 Q. Dr. Chambers, you also mentioned the fecal data was
10 suggestive of a significant growth inhibition. What data
11 leads you to that conclusion?

12 A. Yes, I believe it's in table, it's either 1 or 3.

13 Q. Table 3 I believe at the top of 1166. Is that it?

14 A. Yes, it is.

15 And if you would highlight the total anaerobic
16 counts and doxycycline resistant counts over to three
17 months. Yes, there you go.

18 So you can see at baseline, and these are log
19 values, so I'm going to do an interpolation here to make
20 this understandable.

21 The total anaerobic counts in both the placebo
22 and the doxycycline group at baseline are around 7. That is
23 log 10, 7, and the doxycycline resistance is very similar,
24 log 10, 5.78, and log 10, 5.5. That corresponds to about a
25 three or five percent frequency of resistance in the total

Chambers - direct

1 anaerobic counts.

2 Then if you look over to the three month, in the
3 doxycycline group, you can see that the doxycycline
4 resistant counts are now 7.19 and actually are numerically
5 superior to the total counts, which is mathematically not
6 possible. So that is 100 percent of the organisms are
7 resistant in that subset of patients at three months.

8 And you can see over the placebo to the right
9 that the values from baseline are essentially unchanged in
10 both those variables.

11 So I call this suggestive because there's -- and
12 I commented on this in my deposition initially, that there
13 is some issue with how the statistics were done, and I think
14 there's an error in the table, that I was not able to do a
15 statistical analysis to sort through that, so I just took
16 the values at face value. But I was struck by a hundred
17 percent resistance at three months only in the doxycycline
18 group.

19 Q. Assuming that you were correct, that there is
20 100-percent resistance in the doxycycline group, what
21 conclusion would you draw from that data?

22 A. Well m again, as before, this is an example of
23 significant inhibition of growth in that you've selected for
24 resistance of subpopulation in this case, all the organisms
25 are resistant.

Chambers - direct

1 Q. Did the Walker 2005 study include a positive control?

2 A. No, it did not.

3 Q. What impact does the lack of a positive control have
4 on your ability to scientifically interpret the Walker 2005
5 data to find that there is no significant inhibition of
6 growth?

7 A. It basically again allows you to exclude the false
8 negatives. So if your test method is actually able to
9 detect by the techniques used anti-bacterial effect, you
10 should be able to observe that effect in the positive
11 control group.

12 In the absence of a positive control group,
13 you can't really judge whether this negative, if there is a
14 negative result, it is a true negative or a false negative.

15 Q. In the Walker 2005 data, are you able to rule out the
16 possibilities of a false negative?

17 A. No, I'm not.

18 Q. Let's wrap up the in vivo studies. Can you look at
19 DDX-313?

20 Dr. Chambers, what is DDX-313?

21 A. Yes. These are the summaries of the five studies
22 that we have just gone over. They're listed to the left. I
23 will not go into detail of these. And the specimen
24 analyzed. Three of these analyzed oral flora with
25 subgingival plaque samples. To the extreme right is my

Chambers - direct

1 opinion about evidence of significant inhibition.

2 Four of the six studies I think definitively
3 show evidence of an antibiotic effect. That is, inhibition
4 of bacterial growth.

5 In the Walker study, the stool samples are
6 suggestive of the three-month time point, but I commented on
7 the statistical analysis and not being able to be definitive
8 about that. And the vaginal swab data are insufficient to
9 make a confident assessment about no effect on vaginal
10 flora.

11 Q. Thank you.

12 Let's now turn to the content of Mylan's
13 label. Did you hear Dr. Webster testify that the
14 label describes Mylan's ANDA product as 2001 that will not
15 significantly inhibit the growth of microorganisms?

16 A. He didn't say that exactly. It was words to that
17 effect, yes.

18 Q. Do you agree with Dr. Webster on that point?

19 A. No, I do not.

20 Q. Why don't we take a look at a slide used by Dr.
21 Webster during his testimony, PDX-112.

22 Do you have that in front of you, Dr.
23 Chambers?

24 A. I do.

25 Q. Can you read the highlighted portion that was a

Chambers - direct

1 portion that Dr. Webster said that he interprets to mean
2 that Mylan's ANDA product contains an amount of doxycycline
3 that does not significantly inhibit the growth of
4 microorganisms?

5 MR. FLATTMANN: I object, your Honor. This was
6 not disclosed to us as a slide that was going to be used
7 with this witness with the demonstrative last night.

8 THE COURT: Any response?

9 MR. KONG: He is correct, this was not
10 disclosed. My understanding is that Dr. Webster's testimony
11 was taken for what it was worth and that we could use these
12 slides for purposes of just illustrating what in the label
13 Dr. Webster referred to for his testimony.

14 MR. FLATTMANN: They could have done that, your
15 Honor, and sent us a copy of it last night so we knew he was
16 going to talk about it today. Instead, they're surprising
17 us.

18 THE COURT: I'm going to overrule the objection.
19 If you want to take a recess to prepare your cross, we'll do
20 that.

21 Go ahead and ask the question.

22 MR. KONG: Thank you, your Honor.

23 BY MR. KONG:

24 Q. Could you please read the highlighted portion of the
25 microbiology sections of Mylan's label?

Chambers - direct

1 A. Yes. It reads, "In vivo microbiological studies
2 utilizing a similar drug exposure for up to 18 months
3 demonstrated no detectable long-term effects on bacterial
4 flora of the oral cavity, skin, intestinal tract and
5 vagina."

6 Q. Dr. Chambers, in your opinion, is that excerpt from
7 Mylan's label accurate?

8 A. Yes.

9 Q. Can you please explain to me how on the one hand you
10 say that this excerpt of the label is accurate, yet on the
11 other hand, you also say that Mylan's ANDA product will
12 significantly inhibit the growth of microorganisms?

13 A. I think this is very carefully worded and
14 appropriately so based upon an analysis of the data. The
15 key words are no detectable and long term. This does not
16 exclude the possibility and I think the reality of an
17 antibiotic effect during administration of the drug and drug
18 exposure. It does not address that point. It just makes
19 the point that the effects are not long term.

20 Moreover, it uses the words, no detectable,
21 leaving open the possibility that there might be effects,
22 but they might not have been detected.

23 Q. Now, Dr. Chambers, in your opinion, what insight does
24 the highlighted label excerpt provide regarding whether
25 Mylan's ANDA product will not significantly inhibit the

Chambers - direct

1 growth of microorganisms?

2 A. It does not speak to that issue.

3 Q. Why don't we take a look at PDX-113, which is another
4 excerpt that is highlight here.

5 Could you please read the highlighted portion of
6 Mylan's label for us?

7 A. Yes. It says, "Doxycycline should not be used for
8 treating bacterial infections, providing anti-bacterial
9 prophylaxis or reducing the numbers or eliminating
10 microorganisms associated with any bacterial disease."

11 Q. In your opinion, is that label excerpt accurate?

12 A. Yes, it is.

13 Q. Can you please explain how on the one hand you say
14 that label excerpt is accurate, yet on the other hand you
15 also say that Mylan's ANDA product contains an amount of
16 doxycycline that will significantly inhibit the growth of
17 microorganisms?

18 A. Yes. This is simply the difference between a
19 therapeutic that is full dose of antibiotics that are used
20 to treat a serious infection and the realization that even
21 at subtherapeutic doses, there can be significant growth
22 inhibition in microorganisms. In fact, Dr. Webster himself
23 commented on this when he said that doxycycline
24 50 milligrams once a day was a subtherapeutic dose but had
25 anti-bacterial effect. I say the same thing for

Chambers - direct

1 40 milligrams.

2 Q. And in your opinion, what insight does the
3 highlighted statement provide regarding whether Mylan's ANDA
4 product will not significantly inhibit the growth of
5 microorganisms?

6 A. It does not address that issue.

7 Q. Let's take a look at the next label excerpt that Dr.
8 Webster discussed, PDX-114.

9 Could you please read what has been highlighted
10 here?

11 A. "The plasma concentrations of doxycycline achieved
12 with doxycycline during administration are less than the
13 concentration required to treat bacterial diseases."

14 This is essentially a rationale for the
15 statement that follows, why it is not appropriate for
16 treating bacterial infections. It should also be pointed
17 out that this labeling is for an indication that is not
18 known to be caused by bacterial etiology and that a does
19 that has never been tested clinically and demonstrated to be
20 useful in treating bacterial infections. Therefore, a
21 caution in using this drug for that purpose.

22 Q. In your opinion, is the statement that you just read
23 accurate?

24 A. Yes, it is.

25 Q. Can you explain for us how on the one hand you say

Chambers - direct

1 that this statement is accurate, yet on the other hand you
2 also say that Mylan's product contains an amount of
3 doxycycline that will significantly inhibit the growth of
4 microorganisms?

5 A. Well, I think as the evidence shows, it has
6 concentrations that can significantly inhibit organisms, but
7 these are well below the doses that would be used to treat a
8 bacterial infection.

9 Q. Staying on the subject of the content of Mylan's
10 label, could you please turn to DTX-1336?

11 A. Yes, I have it.

12 Q. What is DTX-1336?

13 A. This is a memo from CollaGenex to FDA.

14 Q. Did you rely on DTX-1336 for your opinions in this
15 case?

16 A. Yes, I did.

17 MR. KONG: Mylan offers DTX-1336 into evidence.

18 MR. FLATTMANN: No objection.

19 THE COURT: It's admitted.

20 (DTX-1336 was admitted into evidence.)

21 BY MR. KONG:

22 Q. Let's turn to GAL125975.

23 What appears there at the top of that page?

24 A. This is the proposed labeling for, I believe it's the
25 Oracea product.

Chambers - direct

1 Q. And what section does that proposed language pertain
2 to?

3 A. The microbiology section.

4 Q. And remind me, what language did we just review from
5 the Mylan label?

6 A. Well, these are two of the statements that have now
7 been modified compared to the original label.

8 Q. I apologize. My question wasn't clear. The
9 highlighted excerpts that we read earlier, where did those
10 come from?

11 A. Oh, the microbiology section.

12 Q. Okay. So what proposed language here on this page
13 stands out to you?

14 A. Well, there's a change that's pretty significant. It
15 says, the plasma concentration achieved. Instead of being
16 not sufficient to treat a bacterial infection, they read it,
17 they propose that it say well below the level required to
18 inhibit microorganisms.

19 And then the second change, instead of no
20 detectable long term effect in the prior label, we now see,
21 no effect as the substituted terminology.

22 Q. And you said prior label. Do you mean the prior
23 proposed language in CollaGenex?

24 A. Yes.

25 Q. Let's now turn next to DTX-1338.

Chambers - direct

1 Dr. Chambers, what is DTX-1338?

2 A. This is a memo from FDA to CollaGenex.

3 Q. Did you rely on DTX-1338 while forming your opinions
4 in this case?

5 A. Yes, I did.

6 MR. KONG: Mylan offers DTX-1338 into evidence.

7 MR. FLATTMANN: No objection.

8 THE COURT: It's admitted.

9 (DTX-1388 was admitted into evidence.)

10 BY MR. KONG:

11 Q. GAL33561, what appears there?

12 A. So this is a statement from FDA on the proposed
13 wording for the clinical microbiology section. Now from FDA
14 to CollaGenex.

15 Q. And what does FDA say in response to CollaGenex
16 proposed label?

17 A. So they first quote the proposed label, that's Item
18 1. The plasma concentration of doxycycline achieved will be
19 below the concentration required to inhibit microorganisms.
20 And they point out under .28, demonstrates no effect. They
21 ask for evidence to support those two claims.

22 Q. If we can turn to DTX-1339, please. What is
23 DTX-1339?

24 A. This is from FDA ruling on the proposed labeling and
25 giving guidance as to what that labeling should be.

Chambers - direct

1 Q. Did you rely on DTX-1339 for purposes of formulating
2 your opinions in this case?

3 A. Yes, I did.

4 MR. KONG: Mylan offers DTX-1339 into evidence.

5 MR. FLATTMANN: No objection.

6 THE COURT: It's admitted.

7 (DTX-1339 was admitted into evidence.)

8 BY MR. KONG:

9 Q. Dr. Chambers, do you have an understanding with
10 regard to what FDA reviewed in advance of creating DTX-1339?

11 A. Yes. They looked at data, they don't refer to them
12 as the publications, but they are the data from the Skidmore
13 study and Walker 2005.

14 Q. And how do you know that?

15 A. Well, when you match the data up, they're exactly the
16 same.

17 Q. How do you know the FDA reviewed the data?

18 A. It's discussed in several of the documents.

19 Q. If you could, please turn to GAL240914.

20 Could you tell me what appears there on that
21 page?

22 A. This is a ruling on what the label has to say.

23 Basically, this is their non-negotiable wording. So they
24 say that they're going to approve the label in the NDA
25 admission provided the applicant makes the appropriate

Chambers - direct

1 changes to the microbiology section of the proposed label.

2 Q. And I understand that you prepared a demonstrative to
3 demonstrate what changes were proposed in that statement
4 there. If we could go to DTX-312.

5 Dr. Chambers, can you tell us what DTX-312 is?

6 A. Yes. So this is a track changes to show what
7 happened to the labeling from the proposed label to what the
8 FDA has suggested would require approval.

9 Q. And what changes here stand out to you?

10 A. So just to orient you, the strike through is what is
11 in the label is omitted. And that's in red. The underline
12 in red is the new wording. And then you can see the
13 strike-through has inhibit microorganisms is gone and now
14 inserted, we have, detect all long term -- term effects.

15 Now it reads, the plasma concentrations of
16 doxycycline achieved with the Oracea during administration
17 are less than the concentration required to treat bacterial
18 infections. Stricken is reference to the concentration
19 required to inhibit organisms.

20 In the second sentence, the microbiologic
21 studies, instead of saying there is no effect, it says, no
22 detectable long term effects on bacterial flora.

23 Q. How is no detectable long term effect different from
24 no effect?

25 A. Well, no effect is a pretty inclusive statement. I

Chambers - direct

1 think this reflects reasonably the evaluation of the data
2 submitted to back this claim, and they were comfortable with
3 the no long term, but were circumspect about I think the
4 detectability, but were comfortable that there were no
5 detectable long-term effects.

6 Q. What is your opinion regarding whether the Skidmore
7 and Walker 2005 studies support the label excerpts that
8 we've looked at today? In other words, the label excerpts
9 that are included in Mylan's ANDA product?

10 A. I think it is a fair interpretation of the label as
11 written in Mylan's ANDA product.

12 Q. Let's turn to DTX-1340.

13 Dr. Chambers, what is DTX-1340?

14 A. This is another memo from CollaGenex to the FDA.

15 Q. Did you rely on DTX-1340 for purposes of forming your
16 opinions in this case?

17 A. Yes, I did.

18 MR. KONG: Your Honor, Mylan offers DTX-1340
19 into evidence.

20 MR. FLATTMANN: No objection, your Honor.

21 THE COURT: It is admitted.

22 (DTX-1349 was admitted into evidence.)

23 BY MR. KONG:

24 Q. If you could turn to Bates number 34431.

25 What language did CollaGenex include for

Chambers - direct

1 inclusion into the label? Two Oracea available.

2 A. Yes. We're in the microbiology section again at the
3 tail end and now a new paragraph.

4 And so trade name here refers to Oracea. I will
5 just read in Oracea.

6 While Oracea has been demonstrated to have no
7 anti-microbial activity, it has been shown in vitro to
8 suppress pro inflammatory processes such as neutrophil
9 activation, inhibition of matrix metalloproteases,
10 endogenous nitric oxide release, and expression of inducible
11 nitric oxide synthase. The clinical significance is not
12 known.

13 Q. Did that proposed language ever find its way into the
14 Oracea label?

15 A. No.

16 Q. Did that proposed language ever find its way in the
17 Mylan label?

18 A. No, it did not.

19 MR. FLATTMANN: Objection, your Honor. It's
20 outside the scope of his expert report.

21 THE COURT: Objection noted.

22 BY MR. KONG:

23 Q. Please turn to DTX-2094.

24 A. Okay.

25 Q. What is DTX-2094?

Chambers - direct

1 A. This is a memo describing the ruling of the FDA on
2 two issues. One is should doxycycline at the 20-milligram
3 dosage form be reviewed as an antibiotic, and then the
4 second question is their opinion as to whether that dose of
5 doxycycline would significantly inhibit bacterial growth in
6 a human.

7 Q. Did you rely on DTX-2094 for purposes of formulating
8 your opinion in this case?

9 A. Yes, I did.

10 MR. KONG: Mylan offers DTX-2094 into evidence.

11 MR. FLATTMANN: No objection, your Honor.

12 THE COURT: It is admitted.

13 DTX-2094 was admitted into evidence.)

14 BY MR. KONG:

15 Q. Dr. Chambers, what is Periostat?

16 A. Periostat is a preparation of doxycycline that was
17 developed for use in treating periodontal disease. It's
18 administered as a 20 milligram, twice daily dose.

19 Q. Does Periostat have comparable drug exposure to
20 Mylan's ANDA product.

21 A. Yes, it does.

22 Q. What scientific issue did FDA address in DTX-2094?

23 A. Whether that amount of doxycycline in Periostat would
24 produce in humans an inhibitory concentration of drug
25 against microorganisms.

Chambers - direct

1 Q. Would you please turn to DTX -- I'm sorry -- page 15
2 of DTX-2094? At the very bottom of that page and spilling
3 over to page 16, what conclusion did the FDA draw regarding
4 Periostat?

5 A. In conclusion, Periostat was administered using a
6 dosage regimen of 20 milligrams or orally twice daily has
7 the capacity to inhibit or destroys strains of bacteria,
8 i.e., microorganisms, susceptible to low concentrations of
9 doxycycline.

10 Q. Does that mean inhibit bacteria in a human?

11 A. Yes.

12 Q. Why do you say that?

13 A. Because you administer Periostat to a human.

14 Q. And what language in the sentence here leads you to
15 believe that administration would be to a human?

16 A. Well, it says Periostat, which is a formulation for
17 humans, when administered, and then they give the dose of,
18 when we're talking about humans.

19 Q. Would you ever administer Periostat to a dish?

20 A. Only if it were sick. No. I would administer
21 doxycycline to a dish.

22 Q. Thank you, Dr. Chambers.

23 Now turning to the doctrine of equivalents, what
24 is your opinion regarding whether Mylan's generic product
25 infringes the Ashley patents under the doctrine of

Chambers - direct

1 equivalents?

2 A. Well, as I understand the doctrine of equivalents,
3 there has to be an equivalent effect so it's fundamentally
4 the same, even though the packaging may look a little
5 different. And in this case we're talking about
6 anti-microbial activity and inhibitory drug effect. So
7 since Mylan's ANDA product has an anti-microbial drug
8 effect, it inhibits bacteria in a human, that cannot be
9 equivalent to a claim that it does not.

10 MR. FLATTMANN: I object to the testimony as
11 outside the scope, your Honor.

12 THE COURT: The objection is noted.

13 BY MR. KONG:

14 Q. In conclusion, Dr. Webster, what is your opinion
15 regarding the safety of Oracea?

16 A. I think it's safe.

17 MR. KONG: Nothing further.

18 THE COURT: Mr. Flattmann, did you want to have
19 a recess in light of the surprise?

20 MR. FLATTMANN: Oh, I think we can proceed, your
21 Honor.

22 THE COURT: All right.

23 MR. FLATTMANN: I appreciate the opportunity,
24 but I think we can proceed.

25 THE COURT: All right. Go ahead, then.

Chambers - cross

1 MR. FLATTMANN: Thank you.

2 CROSS-EXAMINATION.

3 BY MR. FLATTMANN:

4 Q. Good afternoon, Dr. Chambers.

5 A. Hello.

6 Q. Were you here in the courtroom when Dr. Gilchrest
7 testified on direct that the use of 20 milligrams twice
8 daily of doxycycline is sub-anti-bacterial?

9 A. I was here for part of her testimony and I did hear
10 her use that term.

11 Q. And you agree with a her; correct?

12 A. Not in her use of the term in the sense that I'm
13 talking about. I think she's referring to subtherapeutic.

14 Q. Well, she said it was sub-antibacterial. Do you
15 agree or disagree?

16 A. I would have to disagree if she is referring to
17 sub-antibacterial in the way I am talking about.

18 Q. When she was talking about all the prior art
19 references, she said it was sub-antibacterial?

20 A. I think because she is probably using loose
21 vernacular form of the term.

22 Q. All right. But you don't agree with that --

23 A. If she and I are on the same page, definition-wise,
24 we would consider and talk about it. So I don't know what
25 she means when she says it. If she would give me her

Chambers - cross

1 definition, I would be happy to discuss it.

2 Q. All right. But you did hear her say it?

3 A. I did hear her use the term. I'm not certain what
4 she meant about it.

5 Q. It's on the record, I suppose.

6 Now, you would agree one measure of significant
7 inhibitory effect is measurable effect in terms of numbers
8 of bacteria that would grow; right?

9 A. That is one measure, yes. It's not the only one. It
10 is one.

11 Q. It is one, right?

12 A. Yes, it is.

13 MR. FLATTMANN: Okay. And you were looking at
14 the Mylan label, PDX-113.

15 Can we put that back up, please?

16 BY MR. FLATTMANN:

17 Q. The Mylan label states that Mylan's proposed product
18 should not be used for reducing the numbers or eliminating
19 microorganisms; right?

20 A. It doesn't say one word about if it would do it. It
21 says it should not be used for doing it.

22 Q. I asked you whether it said or didn't. Does it say
23 that it should not be used for reducing the number of
24 microorganisms?

25 A. It says it should not be used.

Chambers - cross

1 Q. Okay.

2 A. Not whether it would.

3 Q. That's what Mylan puts in its label as true; correct?

4 A. Yes. It should not be used for reducing or
5 eliminating microorganisms.

6 Q. Now, you, fairly late in your direct examination, had
7 a redline up of a proposed Oracea label. Do you recall
8 that? It is DDX-312.

9 A. Yes.

10 Q. And you highlighted the fact that the words "well
11 below" -- excuse me -- that the words "Oracea during
12 administration is well below" -- if I could read actually --
13 there we go. Let me start over. I'm sorry.

14 You highlighted the fact that the words "well
15 below" were struck in this version of the label; correct?

16 A. Yes.

17 Q. Okay. You don't know what either CollaGenex or the
18 FDA had in mind by the words "well below," do you?

19 A. It's not quantified, no.

20 Q. Okay. Now, another word that is struck out by FDA
21 here. The very first word that is struck out is antibiotic,
22 isn't it?

23 A. Yes.

24 Q. So the FDA struck out the word antibiotic before
25 drugs in the sentence, doxycycline is a member of the

Chambers - cross

1 tetracycline class of antibiotic drugs. It took out the
2 word "antibiotics," didn't it?

3 A. Yes.

4 Q. Okay. Now you are an infectious disease specialist,
5 right?

6 A. I am.

7 Q. And you would not consider rosacea to be one of the
8 infectious diseases included in your specialty area; right?

9 A. No.

10 Q. You are not a dermatologist?

11 A. No.

12 Q. You don't treat patients with rosacea?

13 A. No.

14 Q. And you -- well, you have never treated patients with
15 rosacea; right?

16 A. No.

17 Q. And you don't treat patients with acne; correct?

18 A. One.

19 Q. Your daughter, right?

20 A. Correct.

21 Q. Okay. And your understanding of rosacea is, in your
22 view, pretty minimal because you don't deal with the
23 disease?

24 A. Yes, I would say that I'm not one of the art, if that
25 is what you mean.

Chambers - cross

1 Q. Right. Well, you don't read the literature on
2 rosacea?

3 A. No, I don't.

4 Q. Okay. Now, let me show you a copy of DDX-2091, which
5 is the version of the Mylan label that you looked at at your
6 deposition.

7 A. Okay.

8 MR. FLATTMANN: May I approach, your Honor?

9 THE COURT: You may.

10 (Document passed forward.)

11 MR. FLATTMANN: Here you go, sir.

12 THE WITNESS: Thank you.

13 BY MR. FLATTMANN:

14 Q. Okay. You reviewed this label; correct?

15 A. Yes.

16 Q. Could you please turn to Section 1.2 on page 119687?

17 A. Okay.

18 Q. And if you could look at Section 1.2, please.

19 A. Okay.

20 Q. Are you there?

21 A. I am.

22 Q. Great. And as a 40-milligram capsule taken once a
23 day, you would agree with the statement here in Mylan's
24 label that Mylan's doxycycline capsules should not be used
25 for treating bacterial infections; right?

Chambers - cross

1 A. Not administered as one capsule a day.

2 Q. Okay. You would agree with that statement?

3 A. Yes.

4 Q. Okay. And you agree with the statement that Mylan's
5 40 milligram doxycycline capsule should not be used for
6 reducing the number or eliminating microorganisms associated
7 with any bacterial disease. Right?

8 A. Correct.

9 Q. And if we turn to Section 12. --

10 A. Can we continue in that paragraph?

11 Q. Your counsel can ask you questions, if you would like
12 to, later. He will have that opportunity.

13 A. Okay.

14 Q. Okay? If you could turn to Section 12.4 of the
15 label, that is the microbiology section; right?

16 A. Yes.

17 Q. Okay. And you would agree that doxycycline is a
18 member of the tetracycline class of drugs, as it states
19 here?

20 A. Yes.

21 Q. And you agree that the plasma concentrations of
22 doxycycline achieved during administration with Mylan's 40
23 milligram doxycycline dose once a day are less than the
24 concentrations required to treat bacterial disease; right?

25 A. Yes.

Chambers - cross

1 Q. And you agree with the next statement that Mylan's 40
2 milligram once-a-day doxycycline should not be used for
3 treating bacterial infections, providing antibacterial
4 prophylaxis or reducing the numbers or eliminating
5 microorganisms associated with any bacterial disease; right?

6 A. No, it should not be used for that.

7 Q. So you agree with the statement; correct?

8 A. I do.

9 Q. Okay. And if you look down to the last sentence
10 there: In vivo microbiological studies utilizing similar
11 drug exposure for up to 18 months demonstrated no detectable
12 long term effects on bacterial flora of the oral cavity,
13 skin, intestinal tract and vagina.

14 You understand that the similar drug exposure
15 that they are talking about is 20 milligrams twice-a-day
16 Periostat, right?

17 A. Yes.

18 Q. And you agree with the statement in Mylan's product
19 label that in vivo microbiological studies using a similar
20 drug exposure for up to 18 months in fact demonstrated no
21 detectable long term effects on the bacterial flora of the
22 oral cavity, skin, intestinal tract and vagina; right?

23 A. I agree they are not long term and that they were
24 detectable or not.

25 Q. So you agreed with the statement; correct?

Chambers - cross

1 A. Yes.

2 Q. Okay. Now, let's talk about your opinions regarding
3 the Oracea package insert.

4 Specifically, it's your understanding that
5 during the NDA review process for Oracea, CollaGenex
6 proposed to include a statement in Oracea's label that
7 Oracea does not inhibit microorganisms commonly associated
8 with bacterial diseases; right?

9 A. Correct.

10 Q. And was that in reference to the redline that you had
11 up on the screen before?

12 A. Yes, that was eliminated from the label.

13 Q. And the particular statement that you focused on was
14 the statement that the plasma concentration of doxycycline
15 achieved with this product during an administration is well
16 below the level required to inhibit microorganisms; right?

17 A. I would -- if you could show me the statement, I
18 would be happy to look at it and confirm.

19 Q. I think we can put it back up, again. We just had
20 it. It's PDX -- I lost the number -- 413. There we go.

21 It's DDX-312. Okay?

22 You focused on that statement that you said
23 CollaGenex want to include, namely, that the plasma
24 concentration of doxycycline achieved with this product
25 during administration is well below the level required to

Chambers - cross

1 inhibit microorganisms commonly associated with bacterial
2 diseases; right?

3 A. Correct.

4 Q. Now, I think you already said that you don't know
5 what CollaGenex or FDA meant by the words "well below;"
6 right?

7 A. Well, there is no value given.

8 Q. All right. So it would only be speculation as to
9 what the value would be?

10 A. Well, presumably it's in the range that they define
11 that it achieves; and I think that that is probably what
12 they were referring to, because there are no other
13 concentrations to discuss, are there?

14 Q. You don't know what the range it; right?

15 A. Well, yes. I know what the range is that is achieved
16 with Oracea.

17 Q. You don't know what they mean numerically by "well
18 below," do you?

19 A. Whatever they -- whatever is commonly achieved with
20 the higher dosage form is what they were referring to, which
21 would be several fold above whatever Oracea achieves.

22 Q. Several fold, correct?

23 A. Yes, several fold.

24 Q. But the actual numbers would be speculation on your
25 part?

Chambers - cross

1 A. No, I can give you numbers. I can tell you exactly.

2 Q. Where were the numbers in that document, sir?

3 A. I know it from my knowledge of doxycycline. So if
4 you give 200 milligrams of doxycycline, you will achieve a
5 serum concentration peak of about 2 to 5 micrograms per mil.
6 If you deliver a dose of Oracea, you achieve a peak serum
7 concentration on the order of .6 to .8 micrograms per mil.

8 The trough of doxycycline at 200 micrograms per
9 mil, 1.5 micrograms per mil at 24 hours. It's about
10 0.3 micrograms per mil for the Oracea product, given an
11 equivalent dose 20 milligrams twice a day for the Periostat
12 concentration. That's what is in the label.

13 Q. You looked at a lot of FDA documents. Where does it
14 say what "well below" means?

15 A. Well, you know, it's going to be below whatever that
16 concentration is.

17 I think we're really parsing about "well below"
18 and "below" when I think we know what the levels are because
19 I just gave them to you. You are going to be below those.

20 Q. Did you talk to any former employees of CollaGenex
21 about what "well below" meant?

22 A. No.

23 Q. Or FDA correspondence?

24 A. No.

25 Q. Did you talk to anybody at Galderma about it?

Chambers - cross

1 A. No.

2 Q. Did you talk to anybody at FDA about it?

3 A. No.

4 Q. Okay. And you didn't review any testimony from
5 anybody at FDA about what FDA had in mind?

6 A. No.

7 Q. When they made these changes to the label?

8 A. No.

9 Q. Okay. These are your own opinions; right?

10 A. No. It is based on the facts and concentration that
11 is achieved and knowing what the concentrations are when you
12 deliver therapeutic amount of drug.

13 Q. Um-hmm.

14 A. So I guess the question is what is "well" versus
15 "well below."

16 Q. And do you know as well what FDA meant when it
17 removed the word "antibiotics" from the label in front of
18 the drug?

19 A. It's a more general term.

20 Q. Okay. Now, let's talk about some of the clinical
21 microbiology studies of Periostat that you criticized.

22 Do you have the Skidmore study in front of you,
23 sir? It's PTX-199. If it makes it easier, I can hand you a
24 separate copy.

25 A. I don't know where it is in my binder.

Chambers - cross

1 Q. I'll do that.

2 MR. FLATTMANN: May I approach, your Honor?

3 THE COURT: You may.

4 (Documents passed forward.)

5 MR. FLATTMANN: There you are.

6 BY MR. FLATTMANN:

7 Q. Now, you reviewed this article in the context of
8 providing your opinions on direct; correct?

9 A. I did.

10 Q. And you understand that the study reflected in the
11 Skidmore article was submitted to the FDA as part of the
12 approval process for Oracea?

13 A. Yes.

14 Q. And you agree with the conclusion of Skidmore to the
15 extent that it states that twice daily subantimicrobial
16 doxycycline did not result in an increase in the number of
17 resistant organisms at 4 micrograms per milliliter of
18 doxycycline?

19 A. Within the context of their testing the glabella,
20 yes.

21 Q. You agree?

22 A. For the glabella, yes.

23 Q. And when I asked you -- when my colleague asked you
24 the same question at the deposition, you didn't limit it to
25 the glabella, did you?

Chambers - cross

1 A. Well, that is what the Skidmore study refers to. I
2 think I said within the context of the study, and that is
3 what we're talking about. What is the study studying.

4 Q. Within the context of what the study was studying?

5 A. Well, they studied the glabella, so I don't think
6 they can draw any conclusions about the glabella.

7 Q. But -- I'm sorry.

8 THE COURT: Mr. Flattmann, you are speaking over
9 the witness.

10 MR. FLATTMANN: I apologize, your Honor. I was
11 moving too quickly.

12 THE COURT: Are you done with your answer?

13 THE WITNESS: I am, thank you.

14 BY MR. FLATTMANN:

15 Q. Please turn to page 464 of Skidmore, if you would,
16 please. And if you go all the way down to the last
17 sentence.

18 You agree with that statement in the last
19 sentence that "twice daily treatment with subantimicrobial
20 doxycycline for adults with moderate facial acne for six
21 months significantly reduced the number of acne lesions
22 which is well tolerated, had no detectable antimicrobial
23 effect on the cultivable skin flora and did not result in
24 the emergence of resistant organisms"?

25 A. Yes. For the areas they examined, I agree with that.

Chambers - cross

1 Q. And you are not aware of any critiques of the
2 Skidmore article in the scientific literature?

3 A. No.

4 Q. And the Skidmore study, you would agree, supports the
5 statement in the Mylan label that 20 milligrams of
6 doxycycline given twice daily demonstrates no detectable
7 long term effect on bacteria flora on the skin; correct?

8 A. Yes.

9 Q. I'd like to ask you about the Walker 2005 article
10 next. And I will hand you a copy. It's PTX-202.

11 MR. FLATTMANN: May I approach, your Honor?

12 THE COURT: You may.

13 MR. FLATTMANN: There you are, sir.

14 THE WITNESS: Thank you.

15 MR. FLATTMANN: Sure.

16 (Document passed forward.)

17 BY MR. FLATTMANN:

18 Q. Okay. This is another study that you reviewed and
19 discussed on your direct testimony; correct?

20 A. Yes.

21 Q. And you understand that the FDA reviewed the studies
22 reflected in this article as part of the label claim for
23 Oracea; correct?

24 A. Yes.

25 Q. And you understand that Mylan's label also relies on

Chambers - cross

1 these same clinical studies for the statements that are made
2 in its label claim?

3 A. Yes.

4 Q. All right. Now, in this article, the term SDD, that
5 represents 20 milligrams of doxycycline twice daily; is that
6 correct?

7 A. Yes.

8 Q. Okay. And SDD, therefore, is the doxycycline group
9 here; right?

10 A. Correct.

11 Q. All right. Could you please turn to page 1167 in the
12 first column, last sentence. And the authors state, no
13 apparent statistically significant differences were detected
14 between SDD and placebo treatment at any time.

15 Correct?

16 A. I think that is a very cleverly parsed statement.

17 Q. Okay. Do you see that statement?

18 A. I do see it.

19 Q. All right. And from the data that they present with
20 their statistical analysis, you cannot disagree with that
21 statement; right?

22 A. Well, I point it out, the exceptions I took with it.
23 I wish they had shown the data and how they did the
24 analysis. So I have to agree, there is no apparent -- there
25 might be some inapparent statistically significant

Chambers - cross

1 difference, but here there's no apparent statistically
2 significant difference.

3 Q. There's no apparent statistically significant
4 difference between the doxycycline group and placebo at any
5 time; right?

6 A. That's what it says.

7 Q. All right. Now, let me ask you to look at 1168. I'm
8 sorry. Page 1168, if you would. And there's a statement in
9 the middle column, last paragraph before acknowledgments,
10 where they say, further, these data suggest that a
11 nine-month regimen of SDD, A, did not result in a shift in
12 the normal faecal or vaginal flora, and then it goes on.

13 Do you see that?

14 A. Yes, I do.

15 Q. Okay. And with respect at least to the vaginal flora
16 data, you would agree that the data don't show an effect;
17 right?

18 A. That's true. I do agree with that.

19 Q. And with respect to the faecal flora, you agree with
20 that statement; correct?

21 A. With the qualifier.

22 Q. All right. And you also agree with the statement
23 that these data suggest that a nine-month regimen of SDD,
24 the doxycycline treatment, did not result in the overgrowth
25 or colonization of either flora by opportunistic pathogens;

Chambers - cross

1 right?

2 A. None was detected. Agreed.

3 Q. And you don't disagree with the overall conclusion
4 that these data suggest that a nine-month regimen of SDD did
5 not result in an increase in the number of doxycycline
6 resistant bacteria recovered; right?

7 A. Correct.

8 Q. All right.

9 A. Except for that one point that I made in table 3.

10 Q. All right. Now, with regard to Mylan's label
11 statement that in vivo microbiological studies using a
12 similar drug exposure for up to 18 months demonstrate no
13 detectable long-term effects on bacterial flora of the
14 intestinal tract and vagina, you agree that the Walker 2005
15 article supports that statement at least up to nine months;
16 right?

17 A. Yes.

18 Q. All right. Okay. I'm going to now hand you a copy
19 of PTX-201, the Thomas article version that was marked at
20 your deposition.

21 MR. FLATTMANN: May I approach, your Honor?

22 THE COURT: You may.

23 MR. FLATTMANN: Thank you.

24 (Mr. Flattmann handed an exhibit to the witness
25 and the Court.)

Chambers - cross

1 BY MR. FLATTMANN:

2 Q. Now, this is another article that you discussed on
3 direct examination; is that correct?

4 A. It is.

5 Q. And if we look at the abstract of the article here on
6 the first page, 1472, the last sentence on background reads,
7 "Our four studies assessed whether long term SDD changes" --
8 let me reread that. "Our four studies assessed whether long
9 term SDD changes antibiotic susceptibility of the oral
10 microflora in adults with periodontitis."

11 Correct?

12 A. Yes.

13 Q. And you agree that that was the objective of this
14 paper?

15 A. That is one objective, yes.

16 Q. All right. And you think that the methods that were
17 used in the paper were sufficient to meet that objective; is
18 that correct?

19 A. I think they themselves note on some sampling
20 problems, but overall, yes, there were four studies here.
21 We can go through each one, if you want to.

22 Studies 1 and 2 is what I focused mostly
23 on. Despite the sampling issues, I think their methods were
24 okay.

25 Q. You don't recall having any major issues with the

Chambers - cross

1 methods?

2 A. No.

3 Q. In the result section of the abstract, I'm still on
4 the first page.

5 Please look at the statement, there were no
6 statistically significant differences in the proportion of
7 doxycycline resistant isolates among treatment groups in
8 studies 3 and 4.

9 Do you see that?

10 A. Yes, I do.

11 Q. And you largely agree with that statement?

12 A. I do.

13 Q. Okay. And you also agree with the statement that no
14 evidence of multi-antibiotic resistance was found in studies
15 3 and four; is that right?

16 A. Yes, I do.

17 Q. And you agree with the last portion of the sentence,
18 that no cross resistance in studies 2 and 3 were found at
19 any time point; right?

20 A. Except among the tetracycline class, but, no, not
21 outside that class.

22 Q. Okay. And let's look at page 1481, if you would,
23 please, in the lower right-hand corner. It says in that
24 paragraph, as indicated in study two, SDD was not associated
25 with development of resistance in the marker bacterial,

Chambers - cross

1 actinomyces, SPP isolates, independent of the levels at
2 which doxycycline was administered; right?

3 A. I'm not sure I agree with that statement, but I see
4 it.

5 Q. Well, you agreed with it at your deposition; is that
6 right?

7 A. I don't think I did, because I did a calculation that
8 you guys took exception with about the statistical analysis
9 that I thought should have been conducted.

10 Q. You did. I can show it to you, if you would like to
11 see it. Let me give you a copy of your deposition (handing
12 deposition transcript to the witness). Here you are, sir.

13 MR. FLATTMANN: Two copies (handing deposition
14 transcript to the Court). Thank you.

15 BY MR. FLATTMANN:

16 Q. And if you could please turn to page 110 of your
17 deposition, beginning at line 13 and going through line 20,
18 were you asked the following question and did you give the
19 following answer, sir?

20 "Question: Okay. It says as indicated in study
21 two, SDD was not associated with development of resistance
22 in the marker bacteria actinomyces SPP isolates independent
23 of the levels at which doxycycline was administered.

24 "Answer: Yes, I see that.

25 "Question: Okay. Do you agree or disagree with

Chambers - cross

1 that statement?

2 "Answer: I agree with that."

3 That was your testimony; correct, sir?

4 A. That's what it says.

5 Q. Okay.

6 MR. KONG: For completeness sake, I ask that
7 additional testimony be read into the record.

8 THE COURT: We'll allow you to do that on
9 redirect.

10 BY MR. FLATTMANN:

11 Q. So you agree ultimately that the Thomas 2000 article
12 supports the statement made in Mylan's label, that in vivo
13 microbiological studies utilizing a similar drug exposure
14 for up to 18 months demonstrate no detectable long-term
15 effects on bacterial flora of the oral cavity; right?

16 A. Underscoring the terms, no detectable and long term.

17 Q. Then you agree?

18 A. There was clearly selection for resistance during the
19 period of drug exposure.

20 Q. I didn't ask you about that. I asked you whether you
21 agree with the statement in Mylan's label to that effect.
22 Do you?

23 A. Yes.

24 Q. Okay. Okay. I'm going to ask you now about the
25 Walker study from 2000, which you reviewed on direct. It's

Chambers - cross

1 PTX-200.

2 MR. FLATTMANN: May I approach, your Honor?

3 THE COURT: Yes, you may.

4 (Mr. Flattmann handed an exhibit to the
5 witness.)

6 THE WITNESS: Thank you.

7 (Mr. Flattmann handed an exhibit to the Court.)

8 BY MR. FLATTMANN:

9 Q. Now, you understand that this study was also
10 evaluated during the FDA approval process for Oracea; is
11 that correct?

12 A. If you tell me that, I'm willing to believe it.

13 Q. Okay. Would you please turn to the conclusions
14 section at page 1465 of the article. The conclusion is in
15 the abstract, I should say.

16 A. Okay.

17 Q. And do you see it states, the microbial differences
18 observed were attributed to the anti-collagenase and
19 anti-inflammatory properties of SDD and not to an
20 anti-microbial effect.

21 Do you see that?

22 A. Yes, I do.

23 Q. You understand here that SDD here again refers to a
24 sub anti-microbial dose, doxycycline, 20 milligrams twice a
25 day; correct?

Chambers - cross

1 A. Yes.

2 Q. Okay. And it's your personal opinion that the change
3 in spirochetes in Walker 2000 is due to an antibiotic effect
4 more likely than another effect?

5 A. Yes.

6 Q. All right. But that would be speculation; is that
7 right?

8 A. I know the anti-glycinates and inflammatory
9 properties are speculation. They didn't do any experiments
10 to show that and the antibiotic effect is well demonstrated
11 in doxycycline.

12 Q. You still have your deposition with you, sir?

13 A. I do.

14 Q. Please turn to page 92, starting at line ten.

15 A. Which page?

16 Q. Page 92, please. And starting at line ten and going
17 all the way down to line 25, were you asked the following
18 questions and did you give the following answers.

19 "Question: So the only, if I'm understanding
20 you correctly, the only thing you disagree with in this
21 paper is the conclusion regarding whether spirochetes are
22 due to an anti-microbial and anti-bacterial effect, is
23 there?

24 "Answer: Well, first of all, they say there is
25 no change. I disagree on two levels. One is there's a

Chambers - cross

1 change; and, two, there's an interpretation of the basis of
2 that change. At the very least, there are no data to
3 support that it's not due to an antibiotic effect. They
4 don't do the experiments. It's speculation.

5 "My personal opinion is it is due to an
6 antibiotic effect more likely than another effect.

7 "Question: And that would be speculation as
8 well; correct?

9 "Answer: That would be speculation."

10 A. Actually founded on data, however.

11 Q. That was your testimony; correct?

12 A. Yes, sure.

13 Q. All right. And you believe that the Walker 2000
14 article supports Mylan's statement in the package insert
15 that 20 milligrams of doxycycline given twice a day
16 demonstrates no detectable long-term effects on bacterial
17 flora of the oral cavity; right?

18 A. Yes.

19 Q. All right. Okay. Let's look at the Haffajee
20 article. I think you have that as DTX-2097 in your book.

21 A. You know, I don't know what it is in my book.

22 Q. I'm sorry. Let me -- let me just give you a copy of
23 DTX-2097.

24 A. Okay.

25 Q. And I'm using these copies because they're keyed to

Chambers - cross

1 your deposition transcript.

2 A. Okay.

3 MR. FLATTMANN: May I approach, your Honor?

4 THE COURT: You may.

5 (Mr. Flattmann handed an exhibit to the
6 witness.)

7 THE WITNESS: Thank you.

8 BY MR. FLATTMANN:

9 Q. Okay. So this is the Haffajee reference that you
10 referred to in your direct examination; right?

11 A. Yes, it is.

12 Q. All right. Now, the other four studies we just
13 looked at, Skidmore, the two Walker studies, and the Thomas
14 studies, those were all provided by Mylan to the FDA as part
15 of the label submission; is that right?

16 A. I know two of them were and I've accepted that the
17 other one was as well.

18 Q. You're not aware of Mylan ever providing Haffajee to
19 the FDA in connection with its generic version of Oracea;
20 right?

21 A. No.

22 Q. And you personally never informed the FDA of Haffajee
23 in connection with Oracea or Mylan's generic version of
24 Oracea; right?

25 A. No.

Chambers - cross

1 Q. And you are not aware of Mylan ever asking the FDA to
2 change its label or Galderma's label in light of the results
3 of Haffajee; correct?

4 A. Correct.

5 Q. Now, if you would please turn to page 1249 of
6 Haffajee. The Walker article that we looked at earlier,
7 PTX-202, that's cited here in the Haffajee paper; is that
8 right?

9 A. It is listed as a summary, yes.

10 Q. All right. And in particular, Haffajee states that
11 Walker 2005 examined the effect of nine-month administration
12 of SDD and that there were no changes in the level of
13 resistance species in either the faecal or vaginal samples
14 from the subjects detected after long term SDD
15 administration; is that correct?

16 A. Yes.

17 Q. And, once again, SDD is 20-milligram twice daily
18 doxycycline?

19 A. It is.

20 Q. All right. With respect to the specific cites that
21 were examined in Walker 2005, there's nothing in Haffajee
22 that disputes the resulting conclusions set forth in Walker
23 2005; correct?

24 A. That is correct.

25 Q. And Haffajee does not report any resistance caused by

Chambers - cross

1 doxycycline in faecal or vaginal tissue; right?

2 A. No, it does not.

3 Q. And Haffajee similarly does not report any resistance
4 caused by doxycycline in the skin; right?

5 A. No. They didn't examine it.

6 Q. All right. Now, you criticized some of the other
7 studies for not supposedly having a positive control; is
8 that right?

9 A. Yes.

10 Q. Now, it's true that Haffajee does not compare
11 20-milligram doxycycline twice daily to any higher dose of
12 doxycycline; right?

13 A. That is correct.

14 Q. And it does not compare 20 milligrams of doxycycline
15 to any other tetracycline compound for that matter; is that
16 right?

17 A. Yes, that is correct.

18 Q. All right. Now, on page 154 -- actually, yes, on
19 page 154, Haffajee reports in that bottom right-hand
20 section, indeed, the only statistically significant
21 differences among groups after adjusting to multiple
22 comparisons was observed at the six-month visit for mean
23 counts of *A. Israelii*, *S. Gordonii*, *S. Intermedia*, and *P.*
24 *Gingivalis*, primarily the result of the much higher levels
25 of these species in the SDD group at this time point; right?

Chambers - cross

1 A. It says that. I'm not sure what it's referring to.
2 I think it's to figure 4. I think that's important to
3 determine exactly what experiments they are referring to,
4 but I do think it is figure 4 -- if you want to give me a
5 second, I can confirm that for you.

6 Q. Please do.

7 A. Do you want me to --

8 Q. If you think you can find it, that would be helpful.

9 (Pause while witness reviewed exhibit.)

10 THE WITNESS: No, I can't determine exactly what
11 figure it's referring to. Sorry.

12 BY MR. FLATTMANN:

13 Q. Fair enough. But the article does say here that it
14 attributes these differences among groups that it
15 identifies, the only statistically significant differences
16 among groups to be the result of much higher levels of these
17 bacterial species in the doxycycline group at that time
18 point; right?

19 A. That's what it says.

20 Q. You don't disagree with that statement?

21 A. No.

22 Q. Okay. And if you turn to page 155 -- actually, why
23 don't we look at your chart first that talked about
24 Haffajee. If we go to DDX-304.

25 Okay. In your chart, you have a section here

Chambers - cross

1 where you say the spike in resistance, in percentage of
2 resistance organisms is due to significant inhibition of
3 growth; right?

4 A. Yes.

5 Q. And you believe that that is what Haffajee teaches;
6 right?

7 A. No. I think that's what the data show.

8 Q. But that's not what the Haffajee authors said?

9 A. They weren't discussing that. They're talking about
10 sites. They're not talking about this figure at all.

11 Q. Well, actually, it's not what they said on page 155,
12 is it?

13 A. That's not referring to this figure.

14 Q. Well, on page --

15 A. They are talking about individual species. This is
16 all species combined, the data shown here. There is no
17 species designation of what's in this resistance number of
18 organisms. The section you refer to list a series of
19 organisms. They're not talking about resistance. That
20 statement does not apply to that figure.

21 Q. I wasn't talking about those organisms that we just
22 talked about. I was going to ask you a different question.

23 A. I'm sorry.

24 Q. No problem.

25 You attributed the spike in percentage of

Chambers - cross

1 resistant organisms to significant inhibition of growth;
2 right?

3 A. Yes.

4 Q. Okay. If you go to page 155 of Haffajee, left-hand
5 column, and the sentence beginning with, the data.

6 The Haffajee authors say, the data from the
7 present investigation indicated a similar percentage of
8 resistant isolates pre-therapy and at 12 months post
9 therapy, but the nature of the resistant species could not
10 be determined.

11 Correct?

12 A. They do say that.

13 Q. Okay. So you attribute it to a change --

14 A. But they're talking about another data.

15 THE COURT: Dr. Chambers.

16 MR. FLATTMANN: I didn't ask the question.

17 THE WITNESS: I apologize.

18 THE COURT: You have to wait him for her, and he
19 has to wait for you.

20 BY MR. FLATTMANN:

21 Q. You say it's due to significant inhibition of growth,
22 this resistance. They say the nature of the species can't
23 be determined; right?

24 A. What they're telling you is they do not know which
25 species it is.

Chambers - cross

1 Q. All right.

2 A. They're not saying there is no inhibition of growth.

3 Q. Is that what they say in the next sentence, when they
4 say: the question as to whether the same strains of a given
5 species were resistant pre- and post- therapy to the
6 administered agents or whether new resistant strains or
7 strains resistant to multiple antibiotics had emerged could
8 not be answered? Did you read that?

9 A. That's because they didn't test for it.

10 Q. Right.

11 A. So if we could go back, I think it's important to
12 clarify this figure.

13 Q. I think you answered the question, sir.

14 That's what the Haffajee author said.

15 A. Yes, but you are perverting what they're referring
16 to. They're not referring to that figure, and you have
17 juxtaposed those as if they are. What they're referring to
18 is the distribution of resistant organisms that make up that
19 number, and because they were not able to do the DNA
20 hybridization studies in order to dissect what those
21 resistant organisms, they can't cannot assign a resistance.

22 In figure 7, they use an indirect method to try
23 to do that and they conclude that organisms that are
24 resistant to the drugs used tend to be those that are more
25 predominant during the period of therapy.

Chambers - cross

1 What this assessment is is a total count of all
2 species and a shift in the population. That could occur
3 without any change in the overall number of organisms, and
4 that is due to inhibition of growth. There is no doubt
5 about it.

6 Q. The Haffajee authors don't say that, do they?

7 A. That is not what talking about. You have not read
8 the paper properly.

9 Q. Well, I have read the paper, and they just don't say
10 that, do they, that it's due to significant inhibition?

11 A. Well, you know, I think I am a little bit more
12 prepared to discuss the paper than you are, scientifically.

13 Q. I have no doubt of that, sir.

14 A. Thank you.

15 Q. So let's go back to what they actually said. They
16 said that the nature of resistant species could not be
17 determined, right?

18 A. Yes.

19 Q. Okay. And they said that that they couldn't answer
20 the question as to whether the same strains of a given
21 species were resistant pre- and post- therapy to the
22 administered agents or whether new resistant strains had
23 emerged. Right?

24 A. But that doesn't change the effect there was growth
25 inhibition of the susceptible strains and they were easily

Chambers - cross

1 placed by emergence of resistance of pre-existing numbers in
2 that population of organisms or else it reflects a
3 colonization and overgrowth of resistant organisms from a
4 different species, but it does not change that result that
5 there is emergence of resistance due to inhibition of
6 strains. They just can't tell you which ones because they
7 could not do the DNA hybridization studies.

8 Q. You said there were no other explanation for this,
9 and they posited a couple, didn't they?

10 A. No, they are not explaining that away at all.
11 They're just saying that their precision is they cannot tell
12 you which strains it is.

13 Q. Let me ask you a question about another one of your
14 charts, if we could, please.

15 MR. FLATTMANN: Could we please look at DDX-305
16 again?

17 BY MR. FLATTMANN:

18 Q. Now, I think you described this chart as a
19 hypothetical example.

20 A. I did.

21 Q. Okay. And the first group is the doxycycline group
22 in this hypothetical example?

23 A. Yes.

24 Q. And the group on the bottom is a placebo group?

25 A. Yes.

Chambers - cross

1 Q. So the placebo group, there is no doxycycline
2 applied; right?

3 A. Correct.

4 Q. Okay. There is no selection pressure at all applied?

5 A. Correct.

6 Q. I think you used that term in your direct.

7 A. Yes.

8 Q. Okay. And resistance still emerges; right?

9 A. In the placebo group?

10 Q. Yes.

11 A. No.

12 Q. The doxycycline resistant strain gets bigger; right?

13 A. I just put that in there as a hypothetical to show
14 you the background variation that you can see when you
15 sample population over time. I was just trying to be honest
16 rather than keeping them exactly the same at every time
17 point. I thought it would be instructive to show that there
18 is variation in any sampling scheme over time. But the
19 important point is that variation in no way approaches the
20 major difference in the presence of doxycycline exposure.

21 Q. All right. So it's just a coincidence that you show
22 it getting larger over time, the resistance?

23 A. No, it's not a coincidence. I did it on purpose.

24 Q. All right. Now, you understand that the Court
25 construed "sub-antibacterial amount" to mean "an amount

Chambers - cross

1 that does not significantly inhibit the growth of
2 microorganisms;" correct?

3 A. Yes. In a human, I think.

4 Q. Okay. In your opinion, a specific inhibitory effect
5 would be a measurable effect in terms of the numbers of
6 bacteria that would grow or their rate of growth or their
7 ability to sustain themselves in their host, their ability
8 to persist, their overall properties as an organism and how
9 they would survive, persist, thrive and grow in a human;
10 right?

11 A. Yes.

12 Q. And, in your opinion, alteration of normal metabolic
13 machinery is one measure of inhibition; right?

14 A. Yes, that is an in vitro measure.

15 Q. Do you think that is a little more expansive than the
16 Court's definition?

17 A. No, not if it significantly inhibits growth.

18 Q. Okay. Let me show you a transcript from the Markman
19 hearing in this case on the Ashley patent.

20 MR. FLATTMANN: May I approach, your Honor?

21 THE COURT: You may.

22 MR. FLATTMANN: Thank you.

23 There you are.

24 (Document passed forward.)

25 BY MR. FLATTMANN:

Chambers - cross

1 Q. Did you read this transcript?

2 A. I have never seen it before.

3 Q. So you didn't consider it before forming your opinion
4 as to what substantial inhibition of growth is?

5 A. I have never seen it before so I didn't.

6 Q. Could you please turn to page 100, and the very last
7 sentence carrying over to page 101. Did you take into
8 account that Mylan told the Court at the Markman hearing,
9 "neither does any of that, but for the sentence they select,
10 have anything to do with inhibiting the metabolism. These
11 compounds are measured by inhibiting growth."

12 Did you take that into account?

13 A. I mean I never seen this so how can I.

14 Q. Did you take into account?

15 A. If you give me a second -- I mean if you are telling
16 me if I take it into account, I can tell you that I didn't
17 because I have never seen it.

18 Q. Fair enough.

19 A. Why don't you ask me if I agree with it.

20 Q. Did you take into account in the next paragraph on --

21 A. You know, obviously I didn't. I have not seen this.

22 THE COURT: Dr. Chambers, he has a right to ask
23 you questions.

24 THE WITNESS: I'm sorry.

25 THE COURT: You have to listen to the question

Chambers - cross

1 and answer.

2 Go ahead, Mr. Flattmann.

3 MR. FLATTMANN: Thank you, your Honor.

4 BY MR. FLATTMANN:

5 Q. Did you take into account Mylan's statement to the
6 Court that antibiotic amount is determined by whether or not
7 these things kill bugs, not how they kill bugs?

8 A. No.

9 Q. Okay. Are you aware in his claim construction
10 briefing in this case, Mylan told the Court that "the
11 intrinsic record of the Ashley patents plainly and
12 repeatedly states that the antibiotic effect of tetracycline
13 is measured by whether it inhibits the growth of
14 microorganisms, not whether it inhibits their metabolism"?

15 A. I could agree with that, depending. If it only
16 inhibited their metabolism, I would agree with it. I think
17 it has to inhibit growth. By the way, tetracycline is a
18 bacteriostatic antibiotic, so whoever that person, referring
19 to Kelling, that is a mistake.

20 Q. I'd like to look at the demonstrative that you
21 provided to us last night, DDX-314. It's a copy of the MIC
22 chart, very similar to the one that was in your rebuttal
23 report; correct?

24 A. Yes, it is. It may be the exact same.

25 Q. Maybe some different formatting?

Chambers - cross

1 A. Yes, maybe.

2 Q. Okay. And the MIC range that you list here in
3 column 3, that represents range of minimum doxycycline
4 concentrations that will inhibit the growth of strains
5 within each bacteria species in vitro; right?

6 A. Yes.

7 Q. And the MIC 50 here in the fourth column, that
8 represents the MIC value at which 50 percent of the isolates
9 and in a test population would be inhibited; right?

10 A. Yes.

11 Q. As an example, to help us understand, for *Bacteroides*
12 *forsythus*?

13 A. Yes, *Bacteroides forsythus*.

14 Q. Thank you.

15 A. You're welcome.

16 Q. The MIC 50 is set out at less than .12?

17 A. Yes.

18 Q. And for *P. Gingivalis*, the MIC is set out at
19 .6 micrograms per mil; right?

20 A. Yes, it is.

21 Q. And for *Prevotella intermedia*, the MIC 50 is set out
22 at 0.64 micrograms per mil; right?

23 A. Yes, it is.

24 Q. And for *Staphylococcus aureus*, it's set out at less
25 than .12; right?

Chambers - cross

1 A. Yes, it is.

2 Q. And you would agree with me that for each of these
3 bacteria that we just discussed, they all have an MIC of
4 doxycycline that is less than .6 micrograms per mil, right?

5 A. Yes, they are.

6 Q. And your chart says -- let's see. Your chart says
7 here the Cmax of Mylan's proposed ANDA product is
8 .6 micrograms per milliliter; correct?

9 A. I did say that.

10 Q. All right. So in your opinion, with a half-life of
11 23 hours, the steady state trough concentration for Mylan's
12 proposed ANDA product is approximately, what, .3 micrograms
13 per milliliter?

14 A. Yes, it is.

15 Q. All right. And, in your opinion, the mean serum
16 concentrations for Mylan's ANDA product will range between
17 .6 micrograms per mil at approximately two hours after
18 administration and .3 micrograms per mil at trough?

19 A. Actually, those are the mean values so that is what
20 the mean values will be.

21 Q. Okay.

22 A. The actual range will be much greater.

23 Q. But that will be the mean values?

24 A. Yes.

25 Q. Okay. Now, is it your view that -- it is your view

Chambers - cross

1 that Mylan's product, because of the serum concentration,
2 would significantly inhibit many of the strains of the four
3 bacteria that we just talked about; right?

4 A. I didn't say that.

5 Q. You did at your deposition; right?

6 A. Well, that was in the context of not just looking at
7 ANDA's product and those specific organisms. The point was
8 of what the pharmacokinetic analysis of this would allow you
9 to extrapolate to knowing what the AUC of this compound is
10 and what the AUC is of a therapeutic dose.

11 Dr. Webster correctly noted you can't just take
12 the MIC, and I think he said, and it directly corresponds to
13 in vivo. That is incorrect. The proper modeling of the
14 relationship of the MIC to what happens in vivo in terms of
15 efficacy is based upon pharmacodynamics and the driver of
16 that is whichever PK/PD parameters predicted but in all of
17 those equations is the MIC.

18 So what determines efficacy is, because it's all
19 about drug exposure so it is the drug exposure that you can
20 achieve relative to the MIC. So organisms that have a
21 higher MIC, therapeutically, when you try to treat an
22 infection like that with such an organism engineered into
23 the dosing regimens, is goofing it up from underdosing.

24 So the dosage regimens are deliberately selected
25 to be on the upper end of what dose is going to take care of

Chambers - cross

1 95 percent of people in terms of their pharmacodynamics and
2 95 percent of the strains that they're likely to encounter,
3 so it is over-engineered and backed up, if you will.

4 However, at significantly lower doses, you can
5 still inhibit organisms but you would have an unacceptable
6 failure rate therapeutically. However, you can take that
7 relationship because it's the ratio that determines efficacy
8 and as long as you drop the MIC ten fold, you can drop your
9 drug exposure ten fold.

10 And that was the point of this graph, that
11 there is some organisms on there that are so susceptible
12 that the drug exposures that you would expect from the ANDA
13 product would be well above that required to actually treat
14 infections but certainly to inhibit their growth and to
15 affect a change in how they grow in emergence of resistance.
16 That's the point of that chart.

17 Q. But it really wasn't what I asked you.

18 Isn't it your view that Mylan's product, because
19 of its serum concentration, would significantly inhibit many
20 of the strains of the four bacteria that we --

21 A. It would certainly inhibit many of the strains of the
22 lower susceptibility range. Those that are highly
23 susceptible.

24 Q. In those types of bacteria that we discussed; right?

25 A. Yes.

Chambers - cross

1 Q. Okay.

2 A. As long as their MIC is low enough.

3 Q. Okay. Now, if we look at the MIC chart again,
4 DDX-3114, it sets out a range for *P. gingivalis* of .6 to
5 .125; is that right?

6 A. Yes.

7 Q. So every strain of *P. gingivalis* had an MIC of less
8 than or equal to .125 here?

9 A. Yes. Now, if you are going to make a jump to another
10 clinical trial, then you have to know the MIC is of their
11 isolates in the treatment group, because I don't know that
12 this is a representative *P. gingivalis* MIC or of another
13 clinical group of patients.

14 Q. So it's your opinion that a serum concentration of
15 .6 micrograms per milliliter of doxycycline would very
16 likely significantly inhibit the growth of every strain of
17 *P. gingivalis*; right?

18 A. No, I never said that.

19 Q. You sure did.

20 A. Every strain? No way.

21 Q. Okay.

22 A. Can you show me where I said every strain?

23 Q. I think I can. Let me ask you to take a look at your
24 deposition at page 166, line 6 through line 12. Were you
25 asked the following question, and did you give the following

Chambers - cross

1 answer:

2 "Question: Okay. Just to be clear, it's your
3 opinion that .6 micrograms per milliliter of doxycycline as
4 a serum concentration would inhibit, would significantly
5 inhibit every strain of P. gingivalis.

6 "Is that a fair statement?

7 A. You have to read --

8 Q. Sir, please don't interrupt.

9 THE COURT: Dr. Chambers, there is no question
10 pending.

11 THE WITNESS: I'm sorry.

12 THE COURT: He is working on a question. You
13 will get your chance to answer it. Go ahead.

14 MR. FLATTMANN: I'm sorry.

15 BY MR. FLATTMANN:

16 Q. So you were asked:

17 "Question: It's your opinion that .6 micrograms
18 per milliliter of doxycycline as a serum concentration would
19 inhibit, would significantly inhibit every strain of P.
20 gingivalis.

21 "Is that a fair statement?

22 "Answer: It would significantly inhibit the
23 growth of every strain of P. gingivalis. Very likely."

24 That was your testimony; right?

25 A. That was in the context of strains that satisfied the

Chambers - cross

1 ratio and had a significantly low enough MIC. I did not say
2 it would inhibit every strain of P. gingivalis. It would
3 inhibit strains that had a sufficiently low MIC. That was
4 the context of the discussion.

5 Q. You just told me you never said it and it's right
6 there; right?

7 A. You know, every strain that has a very low MIC is
8 simply not every strain, counsel.

9 Q. All right. And similarly, in your opinion, a
10 concentration of .8 micrograms per mil of doxycycline would
11 significantly inhibit P. gingivalis?

12 A. If it had a sufficiently low MIC.

13 Q. Do you still have PTX-201, the Walker 2000 study, in
14 front of you? Do you have that, sir?

15 A. Oh. If you can show me up here, I'll take a look at
16 it. Oh, here it is.

17 Q. I have given you a lot of paper so I apologize. It's
18 the Walker 2000 article.

19 A. I have that one.

20 Q. I'm sorry for the pile of paper.

21 Now, Walker 2000 involved administration of 20
22 milligrams of doxycycline; correct?

23 A. It did.

24 Q. And you understand that 20 milligrams of doxycycline
25 administered twice a day would have a serum concentration of

Chambers - cross

1 approximately .6 to .8 micrograms per milliliter; right?

2 A. Yes.

3 Q. And as set forth in the Walker 2000 paper, there were
4 no statistically significant differences between the
5 doxycycline group and the placebo treatments, including for
6 the pathogens *P. gingivalis*, *P. intermedia*, and *B.*
7 *forsythus*; right?

8 A. Yes, it says that.

9 Q. And that was also true for the opportunistic pathogen
10 SRA; right?

11 A. Yes.

12 Q. And if you go down on page 1468 in Walker, to the
13 section that begins within differences, within treatment
14 differences, Walker also states that there were no
15 statistically significant differences within the SDD or
16 placebo treatment groups in the SRP and the non-SRP design
17 in any of the following microbial groups, including *P.*
18 *gingivalis*, *P. intermedia*, *B. forsythus* and *S. Aureus*.

19 A. Yes.

20 Q. Do you still have the Haffajee article with you?
21 That is DTX-2097.

22 A. Yes.

23 Q. And if you can please look at figure 1 on page 150.

24 Are you there, sir?

25 A. Okay.

Chambers - cross

1 Q. Okay. And figure 1 is a mean count of species at
2 baseline, two weeks and 3, 6 and 12 months; right?

3 A. Yes.

4 Q. And it includes goes for administration of 20
5 milligrams twice a day of doxycycline; right?

6 A. Yes.

7 Q. And in figure 1 of Haffajee, there was no
8 statistically significant difference in mean counts at any
9 time point for P intermedia after administration of
10 20 milligrams twice a day; right?

11 A. It depends. And this is also what you're looking at
12 as counts over time. So they make a comment in the paper
13 that most of the change occurred at two weeks.

14 So if you go to the next figure, which is
15 more informative, you'll see what the change is at the
16 two-week period because the antibiotics depress the count so
17 much by two weeks, that there was no significant time
18 related change in this article.

19 So there are remarkably little effects of any of
20 these antibiotics given the drug exposure, and this is why
21 it's so important to have a positive control, because
22 Erythromycin and metronidazole are given at gangbuster doses
23 of antibiotic therapy, and you can see that there's really
24 remarkably little change in the flora there.

25 So this is not a very good test for looking at

Chambers - cross

1 antibiotic effect because we know that erythromycin and
2 metronidazole are antibiotics at these doses.

3 Q. I want to try to avoid going back to your deposition
4 again, so I will just try to ask the same question.

5 A. All right.

6 Q. There was no statistically significant difference in
7 mean counts at any time point for administration of 20
8 milligrams of doxycycline twice a day; correct?

9 A. That's their conclusion, yes. Adjusted for multiple
10 comparisons.

11 Q. Right. And there was no statistically significant
12 difference in mean counts at any time point after
13 administration of 20 milligrams twice a day of doxycycline
14 and P. Gingivalis; right?

15 A. Right.

16 Q. Okay.

17 A. Although there is a difference. It just didn't
18 achieve statistical significance. It's a log depression of
19 counts in that graph.

20 Q. Can you please to turn page 156 of Haffajee and look
21 at figure 6, if you would?

22 And this figure sets out the mean percentage of
23 sites colonized by species resistant to four micrograms per
24 ml of doxycycline at baseline?

25 A. Yes.

Chambers - cross

1 Q. And at two weeks and 3, 6 and 12 months and in
2 subjects who had received 20 milligrams twice a day of
3 doxycycline; right?

4 A. Yes.

5 Q. Okay. And, again, with respect to P. Intermedia
6 bacteria, there was no statistically significant difference
7 in the means percentage colonized by species resistant to
8 four milligrams per mill of doxycycline; right?

9 A. That is true.

10 Q. And the same was true for P. Gingivalis, that there
11 was no statistically significant difference in mean percent,
12 just like colonized by species resistant to four micrograms
13 per ml at any time point; right?

14 A. That's correct.

15 Q. And that four microgram per million threshold, that's
16 the same threshold that was used in the Walker, the Skidmore
17 and Thomas articles that we discussed earlier; is that
18 correct?

19 A. Yes.

20 Q. Okay. That's the break point that above which people
21 would agree that you're clinically resistant; right?

22 A. Yes.

23 Q. Okay. And that's a standard defined by the CLSI?

24 A. Actually not. It's defined by organism, but it will
25 do.

Chambers - cross

1 Q. Oh, okay. Which organism?

2 A. It depends on which organism you're talking about,
3 set for each organism.

4 Q. But that's the one for doxycycline?

5 A. No, it's not. It's just the drug. It's just the
6 drug and combination.

7 Q. I see.

8 A. But four will catch anybody you're interested in.

9 Q. Got it.

10 You mentioned the FDA 2003 memorandum in your
11 direct testimony. Do you recall that?

12 A. Which one is that one? Is that the determination of
13 whether an antibiotic tetracycline or doxycycline is
14 antibiotic or not.

15 Q. Whether it should be classified as an antibiotic?

16 A. Yes.

17 Q. Do you recall that?

18 A. I do.

19 Q. Okay. And just as a very basic matter that we may
20 have gotten away from, doxycycline is an antibiotic
21 compound; right?

22 A. It's an antibiotic compound, yes.

23 Q. Okay. It has that structure; right?

24 A. Well, that's what it is.

25 Q. Yes.

Chambers - cross

1 A. Structures don't determine whether you're an
2 antibiotic.

3 Q. All right.

4 A. Once you're in a class, you know, you can't look at a
5 structure and say, oh, that's an antibiotic.

6 Q. I think I've got the right nomenclature. It falls
7 within the class of antibiotics; right?

8 A. Yes. The tetracycline class.

9 Q. All right. Now, I want to look at that FDA memo, if
10 you still have it with you. Let me get it. DTX-2094 in
11 your book. If you could please turn to that.

12 A. I have it.

13 Q. Oh, thank you.

14 And if you go to page 15 of the FDA's memo and
15 look at footnote 25, the FDA notes that in examining the
16 serum concentrations attained in criteria for considering a
17 bacterial isolate susceptible, there is no specific
18 adjustment for the protein bound and free drug fractions of
19 doxycycline; is that right?

20 A. That is true. That's what they say.

21 Q. And you agree with the FDA's determination that there
22 is no specific adjustment for protein bound and free drug
23 fractions of doxycycline that can be made here; is that
24 right?

25 A. Correct. But it's not known how to make them.

Chambers - cross

1 Q. All right. And in preparing your opinions in this
2 case, you considered a January 19th, 2005, memorandum
3 opinion from the case, CollaGenex versus Thompson from the
4 District of Columbia district; right?

5 A. I don't know.

6 Q. You mention it in your opening expert report. I will
7 show you a copy.

8 MR. FLATTMANN: May I an approach, your Honor?

9 THE COURT: You may.

10 (Mr. Flattmann handed an exhibit to the witness
11 and the Court.)

12 BY MR. FLATTMANN:

13 Q. Have you seen this before, sir?

14 A. You know, I don't recall. I may very well have. I
15 just don't recall.

16 Q. Okay. I'm just asking because you cite it in your
17 opening expert report.

18 A. That was a long time ago.

19 Q. Okay. Now, if you could please turn to -- well, are
20 you aware that this Court and the District of Columbia
21 decline to rely on the in vitro data that was presented in
22 the 2003 FDA memo?

23 A. I don't know any of the particulars of that decision.

24 Q. Okay. Could you please turn to page 13 of the
25 exhibit, which I don't think I've identified as PTX-492, and

Chambers - cross

1 look at footnote 14, where the Court states, "The Court
2 declines to rely on the in vitro tests as these results
3 directly contradict testing perform by CollaGenex and
4 accepted in 1998 by the FDA," and there's a citation. "And
5 because the record is unclear as to the reliability of in
6 vitro tests."

7 Do you see that?

8 A. I do.

9 Q. All right. Did you consider that in forming your
10 opinions today?

11 A. Yes, in part, yes. That's why -- that's why the --
12 well, no. This -- not because of this.

13 Q. Okay.

14 A. But because I understand the issue, because of my
15 knowledge of the field.

16 Q. But I thought you just told me you didn't even
17 remember if you had seen it.

18 A. Well, you are asking me did I consider this point,
19 and the answer is yes.

20 Q. All right.

21 A. I consider it because of my knowledge of in vitro
22 testing.

23 Q. All right.

24 A. And I was about to tell you what it led to, but
25 that's okay.

Chambers - cross

1 Q. Well, are you aware that the FDA conducted any in
2 vivo tests that were done by the FDA and cited in its memo?

3 A. I don't recall those specifically.

4 Q. All right. You don't recall them generally either;
5 right?

6 A. I recall the principle. I don't recall these. No, I
7 don't.

8 Q. Okay. There were none, were there?

9 A. I told you, I don't know. I don't recall.

10 Q. Okay. Now, I have a few questions regarding your
11 opinion that in vivo antibiotic effects can be predicted
12 from in vitro measurements. Okay?

13 A. Okay.

14 Q. Now, first, I think you've already said that the term
15 sub-anti-bacterial amount as it's used in Ashley, that's an
16 amount that does not significantly inhibit growth in a
17 human; right?

18 THE COURT: Hold on.

19 MR. FLATTMANN: I'm sorry, your Honor.

20 MR. KONG: I will object. Well outside the
21 scope of direct. Mr. Chambers on direct did not address
22 anything regarding in vitro data.

23 THE COURT: Mr. Flattmann?

24 MR. FLATTMANN: I thought he mentioned in vitro
25 data on several occasions, and I think he said on direct,

Chambers - cross

1 and I was surprised, I think he said it wasn't wholly
2 predicted, but it was partially predicted.

3 THE COURT: I will overrule the objection. Go
4 ahead.

5 BY MR. FLATTMANN:

6 Q. That's a good question. Do you think that in vitro
7 data is predictive of in vivo antibiotic effects anymore?

8 A. Yes, I do. I think you have to know a lot in order
9 to do that, and I tried to explain how one goes about doing
10 that.

11 Q. All right.

12 A. In terms of the table that you presented, given the
13 time allotment that we had, you know, I agree with you.
14 It's tricky business.

15 Q. Okay.

16 A. And I find the in vivo data much more compelling, I
17 think, as we all do.

18 Q. Okay. And MIC data, as you pointed out, is an assay
19 that is performed on bacteria in vitro, and not --

20 A. Correct.

21 Q. You can't do a MIC in a patient because they're not a
22 test tube, I think you said; right?

23 A. Correct.

24 Q. Okay. And the real predictors efficacy come out of
25 in vivo studies?

Chambers - cross

1 A. Yes. And once you have a database, you can use the
2 in vitro data to make good estimates, but ultimately you do
3 have to prove it in an in vivo, sure.

4 Q. There has to be some validation of efficacy in an
5 animal or a human; right?

6 A. Yes, in order to bring into range with those values
7 made, it's true.

8 Q. And there are instances where the therapeutic dose of
9 an antibiotic needs to be significantly greater than the
10 MIC; is that correct?

11 A. Yes.

12 Q. And I think you said --

13 A. Well, not the dose. The dose does not have to be
14 greater than the MIC. The antibiotic exposure has to be
15 sufficient from the dose to provide the required drug
16 exposure, which is a little different from what you said.

17 Q. Well, I was just quoting from the deposition
18 actually. Could you please go to page 56 of the
19 deposition, beginning at line 22, were you asked the
20 question, and did you give the following answer.

21 "Question: Okay. There are instances, however,
22 where the therapeutic dose needs to be significantly greater
23 than the MIC; correct?

24 "Answer: Yes, there are."

25 That was your answer; right?

Chambers - cross

1 A. You know --

2 Q. Well, was that your answer, sir?

3 A. Yes. It was a sloppy answer.

4 Q. All right.

5 A. It --

6 Q. All right. Now, ultimately, at the end of the day,
7 you can do whatever in vitro test you want to do, but the
8 only way to ever determine whether there's an absence of
9 significant inhibition of bacteria in vivo is to test in
10 vivo; right?

11 A. Yes. Ultimately, you have to do that.

12 Q. And that's because of factors that exist in vivo that
13 don't exist in vitro?

14 A. Yes.

15 Q. Things like protein binding?

16 A. Yes.

17 Q. And I think you conducted a study on daptomycin where
18 you found that daptomycin was involved in significant
19 protein binding; right?

20 A. Yes.

21 Q. And what was the level of level of protein binding
22 in --

23 A. I think we calculated 95 percent, but in subsequent
24 calculations, it was probably proven to be incorrect.

25 Q. Right. And the Mylan label tells us that the -- that

Chambers - cross

1 doxycycline has a very high protein binding percentage;
2 right?

3 A. Correct.

4 Q. What is it about?

5 A. Between seven and fifteen percent. I think ten
6 percent is what your level says.

7 Q. Well, actually --

8 A. Maybe twelve. I can't remember. But that's the
9 range reported in the literature.

10 Q. Doesn't it actually say it's closer to 90 percent?

11 A. Oh, protein bound. I thought you were talking about
12 free drug. You're absolutely right. Protein bound is 90
13 percent. Free drug is seven to fifteen. I apologize.

14 Q. And that can significantly impact the ability to
15 predict in vivo effect and in vivo antibiotic effect from in
16 vitro amounts; correct?

17 A. Correct, if you're in a space if you have no idea
18 what the efficacy of the drug is.

19 Q. Okay. Let me show you a copy of PTX-362.

20 MR. FLATTMANN: Before I find that, I will
21 move on, your Honor. Here we are. I'm sorry about that.

22 May I a preach, your Honor?

23 THE COURT: You may.

24 (Mr. Flattmann handed an exhibit to the
25 witness.)

Chambers - cross

1 BY MR. FLATTMANN:

2 Q. Here you go, sir. And this is the Li paper that you
3 discuss in your rebuttal expert report; is that correct?

4 A. I can't remember which report it's in.

5 Q. One of your expert reports; right?

6 A. Yes.

7 Q. All right. And you're a co-author on this?

8 A. I am.

9 Q. All right. And here, you concluded that the protein
10 binding accounted for a twenty fold increase in the MIC of
11 daptomycin; correct?

12 A. What it actually says is you have to in serum, you
13 get the final print. What we showed was you had to have
14 twentyfold greater concentration in the serum for the
15 filtrate of that serum to give you an MIC.

16 Q. All right.

17 A. Similar, close.

18 MR. FLATTMANN: Your Honor, I offer PTX-362 into
19 evidence.

20 MR. KONG: No objection.

21 THE COURT: It's admitted.

22 (PTX-362 was admitted into evidence.)

23 BY MR. FLATTMANN:

24 Q. Now, I just want to talk a little bit about your
25 research again.

Chambers - cross

1 You've never conducted any human clinical trials
2 to determine whether doxycycline administered 20 milligrams
3 twice a day has anti-bacterial effect in humans; is that
4 correct?

5 A. That is correct.

6 Q. And you've never conducted any human clinical trials
7 to determine whether doxycycline administered 20 milligrams
8 twice a day significantly inhibits bacteria in humans; is
9 that correct?

10 A. Correct.

11 Q. And you've never conducted any human clinical trials
12 to determine whether doxycycline administered 40 milligrams
13 once daily has an anti-bacterial effect in humans; is that
14 right?

15 A. That is correct.

16 Q. And you've never conducted any human clinical trials
17 to determine whether doxycycline administered 40 milligrams
18 once daily significantly inhibits bacteria in humans; is
19 that correct?

20 A. That is correct.

21 MR. FLATTMANN: I have no further questions,
22 your Honor.

23 THE COURT: Thank you.

24 Redirect?

25 MR. KONG: Very briefly, your Honor.

Chambers - redirect

1 REDIRECT EXAMINATION

2 BY MR. KONG:

3 Q. Dr. Chambers, up on the screen is DDX-314. Do you
4 see that?

5 A. I do.

6 Q. Did any of your testimony on direct examination rely
7 on the data that appears here in DDX-314?

8 A. No.

9 Q. Does your opinion that the amount of doxycycline in
10 Mylan's ANDA product will significantly inhibit the growth
11 of microorganisms rely on in vitro data?

12 A. No.

13 Q. Mr. Flattmann read a couple of your deposition
14 excerpts.

15 MR. KONG: For the sake of completeness, I
16 would like to read some follow on lines, your Honor.

17 THE COURT: Well, ask him questions first.

18 MR. KONG: Sure.

19 BY MR. KONG:

20 Q. With regard to your statements regarding P.
21 gingivalis, do you recall that?

22 A. I do.

23 Q. Let me ask a better question than that. On
24 cross-examination, Mr. Flattmann was asking you about
25 whether or not you could use in vitro data to determine

Chambers - redirect

1 whether or not every strain of P. gingivalis would be
2 inhibited.

3 Do you recall that?

4 A. I do.

5 Q. And is it your opinion that you can use in vitro data
6 to determine whether or not every strain of P. gingivalis
7 can be inhibited?

8 A. Obviously not.

9 Q. And do you think you said, you expressed that at your
10 deposition?

11 A. No. It was in the context of discussing
12 pharmacodynamics, and that if a strain had a low enough MIC,
13 that you could inhibit, you would expect to inhibit every
14 strain.

15 Q. Do you recall your deposition testimony?

16 A. I would have to look it up. I don't recall at all.

17 Q. Do you want me to refresh your recollection?

18 A. Yes.

19 Q. Page 166, line 6, is where Mr. Flattmann began
20 reading.

21 If you could look at beginning at line 13 as
22 well. I will read the answer, the last answer that
23 Mr. Flattmann read.

24 "Answer: It would significantly inhibit the
25 growth of every strain of P. gingivalis very likely.

Chambers - redirect

1 "Question: Okay. Answer: That's within the
2 wobble -- you know, here is why I am. First of all, the
3 reason why I wobble on this is I can't help it because I am
4 a scientist type. But, you know, an MIC is a twofold
5 dilution, so if the MIC is .125, it could be .25 if you were
6 to repeat the test again, although, you know, I don't know
7 what the details of their method. And, of course, as the
8 MIC goes up and you factor in, we need to talk about, and we
9 didn't, where the *P. gingivalis* is hanging out and what the
10 local concentration is, because the serum concentration is a
11 guide to that; right?

12 "Question: Okay.

13 "Answer: And so saying every strain causes --
14 you know, it's a little bit too inclusive for me.

15 "Question: Sure. So let me restate that a
16 little bit, then. It's your opinion that administration of
17 doxycycline in a serum concentration of .6 micrograms per
18 milliliter would significantly inhibit most, if not all,
19 strains of *P. gingivalis*.

20 "Answer: Yeah, a significant proportion,
21 however you want to define it. Probably more than one.

22 "Question: Okay. Answer: Based on the MIC,
23 that's what I would predict."

24 Does that refresh your recollection regarding
25 your deposition testimony?

1 A. Yes, it does.

2 Q. Do you agree with that testimony?

3 A. I do.

4 MR. KONG: That's all I have.

5 THE COURT: Fine. You can step down, doctor.

6 Let's take our afternoon break. We'll be back
7 in 15 minutes.

8 (Brief recess taken.)

9 THE COURT: Call your next witness.

10 MR. REED: Thank you, your Honor. We call
11 Robert Skidmore. In connection with Mr. Skidmore's
12 testimony, there is discussion of a document that has
13 already been admitted, PTX-394.

14 THE COURT: About how long is this?

15 MR. REED: Two minutes.

16 THE COURT: All right.

17 MR. REED: At the same time, I would like to
18 call Robert Ashley. In connection with his testimony, we
19 move for the admission of Exhibit DTX-1034.

20 THE COURT: Is there any objection?

21 MS. WILGOOS: I don't have a copy of it, but I
22 don't think there is any objection.

23 (Counsel confer.)

24 MS. WILGOOS: No objection, your Honor.

25 THE COURT: Okay. That exhibit is admitted.

Skidmore - designations

1 (DTX-1034 received into evidence.)

2 THE COURT: About how long is Mr. Ashley?

3 MR. KONG: Mr. Ashley's deposition is about six
4 and-a-half minutes. I have binders for the Court.

5 THE COURT: Okay. Please pass them up.

6 (Binders passed forward.)

7 (Deposition of Robert Arthur Skidmore played.)

8 "Question: Okay. Could you please state and
9 spell your name for the record, please?

10 "Answer: Yes, sir. My name is Robert Arthur
11 Skidmore, junior. R-O-B-E-R-T A-R-T-H-U-R
12 S-K-I-D-M-O-R-E, coma, J-R.

13 "Question: I'm handing you a copy of a paper
14 entitled, Effects of Subantimicrobial Doses Doxycycline in
15 the Treatment of Moderate Acne that was produced at Bates
16 range Galderma 0099991 through GAL 0099996.

17 "Sir, are you familiar with this document?

18 "Answer: I am familiar with the publication
19 Effects of Subantimicrobial Dose of Doxycycline in the
20 Treatment of Moderate Acne published in the Archives of
21 Dermatology.

22 "Question: You're the lead author of this;
23 correct?

24 "Answer: I am the lead author.

25 "Question: So were you primarily responsible

Ashley - designations

1 for drafting the document?

2 "Answer: No.

3 "Question: Who was primarily responsible?

4 "Answer: I don't know. I received a rather
5 finished draft.

6 "Question: So in summary, your understanding or
7 your knowledge of the comments section is restricted to the
8 efficacy of the drug in reducing lesions?

9 "Answer: Yes, sir.

10 "Question: Actually, one follow-up. Before we
11 start on that, just to be clear, then, the rest of the
12 comments, conclusions drawn in the comments section of the
13 Skidmore paper, then, came from CollaGenex; correct?

14 "Answer: I don't know who wrote it. I know
15 that I did not.

16 (Designations of Mr. Skidmore end.)

17 * * *

18 (Deposition designations of Mr. Ashley played.)

19 "Question: Good morning, Mr. Ashley. Could you
20 please state your name for the record?

21 "Answer: Robert Ashley.

22 "Question: Well, what did you mean by, when you
23 said in your patent here, antibiotic dose?

24 "Answer: That dose which would yield a serum
25 concentration sufficient to have -- a systemic

Ashley - designations

1 concentration, plasma concentration sufficient to have
2 significant antimicrobial activity.

3 "Question: Okay. What does that serum
4 concentrate -- what is that serum concentration for
5 doxycycline?

6 "Answer: It was our understanding at the time
7 and my understanding still that that's 1 microgram per mil.

8 "Question: And what is that understanding based
9 on?

10 "Answer: I don't recall.

11 "Question: You said it's your understanding
12 still.

13 "Answer: Um-hmm.

14 "Question: But you don't have a basis for that
15 understanding?

16 "Answer: I don't have a specific basis for that
17 understanding. It was clearly our understanding at the time
18 from a review of the literature and a review of -- and
19 discussion with experts in the field, but I don't recall
20 specifically now.

21 "Question: Do you recall any literature?

22 "Answer: No.

23 "Question: Do you recall any experts with whom
24 you discussed?

25 "Answer: Not specifically.

Ashley - designations

1 "Question: Generally?

2 "Answer: Discussions took place with experts in
3 the field of -- of antimicrobial therapy, but I don't recall
4 specifically who may have suggested that the 1 microgram per
5 mil number was the right number; but that was the number
6 which we understood at the time and, as far as we were
7 concerned, was generally understood as the minimum
8 significant -- the minimum serum concentration which yielded
9 significant antimicrobial activity.

10 "Question: Did you provide any of the
11 literature or summarize the communications with experts to
12 the FDA?

13 "Answer: To the FDA?

14 "Question: In describing what the -- the
15 significance of -- or the basis of the 1 microgram per
16 milliliter?

17 "Answer: I don't recall.

18 "Question: Turning back to what's been marked
19 as Ashley Exhibit 12, column 5, lines 53 to 57, please, sir.

20 "Answer: Okay.

21 "Question: You will notice that it provides
22 some examples of maximum nonantibiotic doses. Do you see
23 that, sir?

24 "Answer: Um-hmm.

25 "Question: Did you contribute those values to

Ashley - designations

1 your patent?

2 "Answer: I don't recall.

3 "Question: Okay. When did you conceive of
4 treating acne by administering an anti -- an antibiotic
5 tetracycline compound in a sub-antibacterial amount that
6 reduces lesion count?

7 "Answer: I don't recall.

8 "Question: But it was it before the April 12th
9 signing of the final protocol that we reviewed earlier?

10 "Answer: Yes.

11 "Question: Okay. And what kind of acne did you
12 conceive of treating?

13 "Answer: Well, I'm not a dermatologist, so my
14 understanding of acne was perhaps cruder at the time, but
15 my -- I was anticipating the treatment of common papular and
16 pustular acne, and acne rosacea.

17 "Question: Yeah. It's the same question that
18 I asked you earlier, sir. Was it your understanding on
19 September 7th, 2004, the date that this document was
20 filed with the Patent Office, that the general knowledge
21 in the prior art was that acne is caused by bacteria, i.e.,
22 P. acne?

23 "Answer: It certainly is my knowledge that the
24 general knowledge in the prior art that was that acne was
25 caused by bacteria. Yes. Do I believe that statement is

Ashley - designations

1 true? I don't know.

2 "Question: That acne is caused by bacteria?

3 That's your understanding?

4 "Answer: The general knowledge in the prior
5 art. My understanding is that the general knowledge in the
6 prior art was that P. acne had a role in acne. Let's say
7 that.

8 "Question: Okay.

9 "Answer: I don't think that causality has ever
10 been proven one way or the other, so I don't know the answer
11 to that question.

12 "Question: So when you said those compounds
13 where there is some demonstrable antimicrobial activity in
14 vivo, doesn't that include doxycycline?

15 "Answer: Right. So that's what I'm saying.

16 "Question: So --

17 "Answer: So the --

18 "Question: So in vitro?

19 "Answer: The pertinence --

20 "Question: -- would be relevant?

21 "Answer: No, no. The opposite. The pertinence
22 of the in vitro data is demonstrably not relevant.

23 "Question: How so?

24 "Answer: Because there is clearly a dose, as
25 we've demonstrated, the subantibacterial or subantimicrobial.

Ashley - designations

1 And there may or may not be for minocycline and for
2 tetracycline and for -- we didn't study those compounds in the
3 same way. But there's a dose which is antimicrobial and
4 there's a dose which is subantimicrobial in vivo, in humans,
5 and that's what we invented or defined was a subantimicrobial
6 dose in humans.

7 "Question: And have you established that it has
8 no antimicrobial effect against any microbe, any
9 microorganism in any location in a human?

10 "Answer: We established that it has no
11 antimicrobial effect. To the extent that we were able to
12 measure it, we were never able to demonstrate an
13 antimicrobial effect.

14 "Question: So your testimony then is that it's
15 antimicrobial to the extent of your testing?

16 "Answer: I think everything -- in any case,
17 that would be true, but, yes, it is antimicrobial. I don't
18 know whether there are effects on microorganisms that we
19 didn't measure. I have no way of knowing that, have I? I
20 have no way of knowing that. I don't know.

21 (Deposition designations end.)

22 THE COURT: You can call your next witness.

23 MR. REED: Thank you, your Honor. Mylan calls
24 Dr. Richard Robbins.

25 RICHARD ALLEN ROBBINS, having been first duly

Robbins - direct

1 sworn, was examined and testified as follows:

2 THE COURT: Good afternoon, Dr. Robbins.

3 MR. REED: Binders, your Honor?

4 THE COURT: Yes.

5 Good afternoon.

6 THE WITNESS: Good afternoon.

7 (Binders passed forward.)

8 DIRECT EXAMINATION

9 BY MR. REED:

10 Q. Dr. Robbins, will you please introduce yourself to
11 the Court?

12 A. My name is Richard Allen Robbins. I'm a, or I was
13 until Saturday, a practicing pulmonary and critical care
14 doctor in Phoenix, Arizona. I retired this past Saturday.

15 Q. Congratulations.

16 A. Thank you.

17 Q. Are you testifying as an expert witness for Mylan?

18 A. I am.

19 Q. Please summarize your education for the Court.

20 A. I received a BS and MD degree in 1976 from the
21 University of Nebraska Medical Center.

22 I subsequently went on and took Internal
23 Medicine training at the University of Missouri at Kansas
24 City for three years, and subsequently did pulmonary and
25 critical care fellowships at two places. One was the

Robbins - direct

1 University of Nebraska Medical Center and the other was the
2 National Institutes of Health in Bethesda, Maryland.

3 Q. Have you received any board certifications?

4 A. I am board certified in Internal Medicine and
5 Pulmonary Medicine.

6 Q. What did you do after your education and
7 certifications?

8 A. After I completed my fellowship, I joined the faculty
9 at the University of Nebraska Medical Center where I was an
10 assistant, later an associate, and finally a full professor
11 until 1996.

12 There was a one year hiatus where I did a
13 sabbatical at the University of London, at the National
14 Heart and Lung Institute.

15 Subsequently in 1996, I left the University of
16 Nebraska Medical Center and became Vice Chairman of the
17 Department of Medicine at Louisiana State University in
18 Shreveport, Louisiana where I was also Professor of Medicine
19 and Physiology.

20 In 1999, I left LSU and went to the University
21 of Arizona, first at the Tucson VA and then subsequently at
22 Phoenix beginning in 1993.

23 Since 1993, I have been the Chief of Pulmonary
24 and Critical Care at the Phoenix VA Medical Center and also
25 since 2005, I've been the fellowship director both at Good

Robbins - direct

1 Samaritan Hospital and the Phoenix VA.

2 Q. You said that you started in Phoenix in 1993? Was
3 that supposed to be --

4 A. Oh, I'm sorry. That was 2003. I misspoke.

5 Q. Please tell us about your academic based medical
6 practice.

7 A. Until Saturday, I did several things that were
8 academically based. First of all, I was a practicing
9 physician. I took care of patients in the hospital, the ICU
10 and also the clinic.

11 I was also a teacher. I taught medical
12 students, residents and fellows.

13 I also was a researcher. I did a combination of
14 both clinical and basic science or bench-type research.

15 Q. To what extent has your work and your research
16 included analysis of nitric oxide and nitric oxide synthase?

17 A. We have been involved in the research regarding
18 nitric oxide and nitric oxide synthases since very early
19 after it was discovered as a biologically active molecule.
20 This goes back to probably 1990 or so.

21 Q. Please describe the grants that you have received to
22 support your laboratory research?

23 A. We received over 20 grants, many of which have to do
24 with nitric oxide and nitric oxide synthase, and these
25 include grants from the National Institutes of Health, the

Robbins - direct

1 Veterans Administration and American Lung Association.

2 Q. Please describe your publications.

3 A. I accomplished over 130 peer-reviewed articles, many
4 which deal with nitric oxide, and a number of book chapters
5 and editorials.

6 Q. Have any of your publications stood out in the field
7 of nitric oxide research?

8 A. I think there are a couple. One is a publication
9 that was in Lancet in 1994 I believe using exhaled nitric
10 oxide in asthma.

11 Another is a paper -- two papers published in
12 BBRC that determined what the nitric oxide comes from, which
13 is the bronchial epithelium.

14 Q. Please describe your role as a peer reviewer and as
15 an editor for scientific journals?

16 A. I'm a peer reviewer for a number of journals, at
17 least 20 or 25 in the last couple of years, and very
18 recently I assumed the role as the editor of the Southwest
19 Journal of Pulmonary and Critical Care.

20 Q. Please describe your activities as a member of
21 professional organizations.

22 A. I'm a member predominantly of two organizations that
23 I am active in. One is the American Thoracic Society. I am
24 the Arizona representative to ATS council, and have been so
25 for a number of years. I have also served on a number of

Robbins - direct

1 committees within the American Thoracic Society.

2 The second organization that I have been active
3 in is the American College of Chest Physicians, and I'm
4 recently elected as the governor for Arizona.

5 Q. Please look at DTX-2168 in your witness binder.

6 A. 2168.

7 Found it.

8 Q. Is this a copy of your CV?

9 A. It is.

10 Q. Is this an accurate summary of your education and
11 experience?

12 A. It is.

13 MR. REED: I offer exhibit DTX-2168.

14 MS. WILGOOS: No objection, your Honor.

15 THE COURT: It's admitted.

16 (DTX-2168 received into evidence.)

17 MR. REED: Your Honor, at this time we offer
18 Dr. Robbins as an expert in the area of nitric oxide and
19 inducible nitric oxide synthase as well as the inflammatory
20 effects of antibiotics, including doxycycline, on those
21 substances.

22 MS. WILGOOS: No objection, your Honor.

23 THE COURT: So recognized.

24 BY MR. REED:

25 Q. Dr. Robbins, what were you asked to do in this case?

Robbins - direct

1 A. I was asked to review the Amin patents that had been
2 discussed earlier and formulate opinions regarding the
3 validity of such patents.

4 Q. Will you please summarize your opinions?

5 A. The following slide is a summary of the opinions.

6 First, Mylan does not infringe the Amin patents
7 because there is no evidence that 40 milligrams of
8 doxycycline administered daily decreases endogenous nitric
9 oxide production or inhibits inducible nitric oxide synthase
10 expression.

11 Second, Mylan does not infringe the Amin patents
12 because there is no evidence of a link between increased
13 nitric oxide production and/or inducible nitric oxide
14 synthase expression and the papules and pustules of rosacea.

15 Third, the prior art in August 1996 inherently
16 anticipates the Amin patents, which merely recognize the
17 inherent property of a tetracycline to decrease nitric oxide
18 production and inhibit inducible nitric oxide synthase
19 expression. And,

20 Fourth, the Amin patents do not enable one of
21 skill in the art to determine a dose of tetracycline that
22 has substantially no antibiotic activity and that also
23 decreases nitric oxide production or inhibits inducible
24 nitric oxide synthase expression.

25 Q. In addition to the Amin patents, what else did you

Robbins - direct

1 consider in forming your opinions?

2 A. I considered a number of things in addition to the
3 Amin patents. These include the Amin patent's file history
4 and other procured documents, the understanding of one of
5 ordinary skill in the art, the Court's claim construction,
6 the applicable legal principles, the scientific literature,
7 the plaintiff's expert's opinions, and my own education,
8 experience and knowledge. For several of these, I also
9 considered the package inserts for Oracea and Periostat.

10 Q. By way of general background, I guess, maybe we're
11 all getting familiar enough with it, but can you tell us,
12 what is nitric oxide and inducible nitric oxide synthase, or
13 iNOS?

14 A. As we heard yesterday, nitric oxide is a gas
15 consisting of one nitrogen and one oxygen atom. However, it
16 is very short lived in the body after being produced and
17 rapidly becomes nitrite or nitrate.

18 On the bottom of this slide is an illustration
19 of how this occurs. Amino acid arginine is converted by a
20 group of enzymes called nitric oxide synthases into
21 citrulline and nitric oxide. We illustrate one of the
22 proteins here that's being discussed today in this patent
23 called the inducible nitric oxide synthase protein. The
24 nitric oxide is then converted either into nitrate or
25 nitrate.

Robbins - direct

1 Q. Can you please explain what happens with ions in an
2 inflammatory situation?

3 A. In most instances, the inducible nitric oxide
4 synthase is not expressed in human cells. An inflammatory
5 stimulus causes activation of cytokines, which then induce
6 the iNOS gene, which leads to expression of the iNOS
7 protein, leading to the production of more nitric oxide.

8 Q. Is inducible nitric oxide, synthase, expressed in
9 inflammatory diseases?

10 A. Yes.

11 Q. Can you give us some examples is of inflammatory
12 diseases in which iNOS expression is increased?

13 A. Well, two well-known examples would be rheumatoid
14 arthritis and periodontitis.

15 Q. Can you give us an example of an inflammatory disease
16 in which iNOS expression is not increased?

17 A. Well, one of these appears to be rosacea.

18 Q. We'll hear your reasons for your opinion that there
19 is no evidence of a link between iNOS expression and nitric
20 oxide and the papules and pustules of rosacea, but, first,
21 let's go over your first infringement, excuse me, your first
22 opinion regarding infringement.

23 What opinion did you form regarding a
24 40-milligram daily dose of doxycycline?

25 A. That Mylan does not infringe the Amin patents because

Robbins - direct

1 there is no evidence that 40 milligrams of doxycycline
2 administered daily decreases endogenous nitrous oxide
3 production or inhibits iNOS synthase expression.

4 Q. What did you do to form this opinion?

5 A. I reviewed the pertinent scientific literature, my
6 own research, education and experience, Amin patents and the
7 other documents I outlined in a previous slide.

8 Q. Did you consider the Court's claim construction?

9 A. Yes, I did.

10 Q. Is this the same approach you took to forming each of
11 your opinions?

12 A. Yes, it was.

13 Q. Now, one of the things you said that you reviewed was
14 the Amin patents. Let's look -- take a look at the three
15 independent claims being asserted by Galderma.

16 What do these three claims have in common?

17 A. Each involves nitrous oxide or nitric oxide synthase
18 with claim 1 and 11 from the Amin patents being involved in
19 nitric oxide production, and claim 1 from the '775 patent
20 being involved in inducible nitric oxide synthase
21 expression.

22 Q. So this is the common limitation of all three
23 independent claims. What does that mean about the dependent
24 claims?

25 A. The dependent claims all fall from these independent

Robbins - direct

1 claims.

2 Q. What do you understand about the limitations of the
3 independent claims being included in the dependent claims?

4 A. I'm sorry. I don't understand the question.

5 Q. Do you understand that the limitations of the
6 independent claims are included in the dependent claims?

7 A. Yes.

8 Q. Okay. We'll come back to the patents, the Amin
9 patents in just a minute, but first let's consider the
10 accused Mylan product.

11 What is the amount of doxycycline that is
12 administered daily for Mylan's product?

13 A. 40 milligrams once daily.

14 Q. And what is the amount of doxycycline that is
15 administered for Galderma's Oracea product?

16 A. 40 milligrams once daily.

17 Q. And what is the steady state Cmax achieved by
18 administering 40 milligrams of doxycycline daily?

19 A. According to the Oracea package insert, the Cmax is
20 600 nanograms per milliliter with a standard deviation given
21 here. That equates to .6 micrograms per milliliter.

22 Q. Can you very briefly describe what Cmax means?

23 A. The Cmax in the steady state level in this case means
24 after administering 40 milligrams daily of the doxycycline,
25 this was the maximal concentration achieved in the blood

Robbins - direct

1 plasma after the seventh, or after the seventh dose.

2 Q. Now let's consider the Amin patents again. You
3 understand that the Amin patents describe some studies in
4 which tetracyclines were administered at different
5 concentrations; right?

6 A. That's correct.

7 Q. What concentrations of tetracyclines were examined in
8 the studies described in the Amin patents?

9 A. They use two drugs. One is doxycycline. The other
10 is minocycline. And the concentrations used were from 5 to
11 80 micrograms per milliliter.

12 Q. Did the Amin patent researchers perform any in vivo
13 studies that are reported in the patents?

14 A. They did not.

15 Q. What studies are described in the Amin patents?

16 A. These are in vitro studies.

17 Q. Of the examples in the Amin patents, which are the
18 most relevant to your opinions?

19 A. I'm going to talk about examples 2 and 3, I believe.
20 There are other examples in the patents. However, these
21 don't discuss the dose range that I'm going to talk
22 about.

23 Q. Okay. Let's look at Example 2.

24 Will you please describe for us the
25 experiment you conducted in Example 2?

Robbins - direct

1 A. Example 2 is act actually an ex vivo study. It's a
2 human using human osteoarthritis affected cartilage from
3 patients undergoing knee replacement surgery. It's minced
4 and then digested and then cell suspension cultured.

5 These cell suspensions are then treated
6 with 5 to 80 milligrams per milliliter of doxycycline or
7 minocycline.

8 Measurements were taken at 24, 48 and
9 72 hours. The measurement that was performed was nitrite,
10 which would be a measure of nitric oxide.

11 The results are displayed in figures 1A, 1B and
12 1C of the Amin patents.

13 Q. Before we look at those figures, can you explain why
14 it's appropriate to measure nitrite?

15 A. Nitric oxide can be quite difficult to measure. It
16 is a short lived molecule. Therefore, what one does is
17 measure the more stable end product of the nitric oxide
18 production, which is nitrite predominantly in cell cultures.

19 Q. Looking at figures 1A, 1B and 1C in the Amin patents,
20 will you please describe the results?

21 A. Each of these figures shows the production of nitrite
22 at different time points and under different concentrations
23 of doxycycline and minocycline. In each figure, the nitrite
24 released from the cell suspensions is on the vertical axis,
25 and the amount of minocycline or doxycycline is on the

Robbins - direct

1 horizontal axis.

2 The panel on the left represents the results at
3 24 hours and the center at 48 hours, and on the far right at
4 72 hours.

5 As you can see that each of these, both the
6 doxycycline and the minocycline, causes a dose dependent
7 inhibition of the production of nitrite from these cartilage
8 cells.

9 Q. What did you mean by a dose dependent response?

10 A. Well, what happens, as you increase the concentration
11 over the range tested, there appears to be increasing
12 inhibition of the nitrite production.

13 Q. And from these data points that are on the figures
14 from example 2 of the Amin patents, what concentrations of
15 doxycycline had the effect of reducing nitrite?

16 A. In each of these panels, the control, or the amount
17 produced with no doxycycline or minocycline, is given by the
18 dot or triangle slightly underneath it on the far left-hand
19 portion of the figure.

20 The amounts with increasing doxycycline
21 represented by the closed triangles or minocycline by the
22 closed circles are given as follows. What one sees as one
23 increases the amount of doxycycline or minocycline added,
24 there appears to be a point that when one can demonstrate
25 inhibition of nitrite production by these cells. That

Robbins - direct

1 point appears to be at least above ten micrograms per
2 milliliter, and perhaps in a couple of these figures, even
3 higher, at 20.

4 Q. Please remind us again, what is the Cmax achieved by
5 a 40-milligram daily dose of doxycycline?

6 A. The Cmax for 40 milligrams of doxycycline is
7 0.6 micrograms per milliliter.

8 Q. Did you prepare an illustration of where that
9 concentration would fall on figure 1A?

10 A. I did and it is shown on the following slide. This
11 shows -- this is figure 1A from the previous set of slides.
12 It shows nitrite released from the cells on the vertical
13 axis and the concentrations of doxycycline or minocycline.

14 We added in a yellowish type of line to
15 illustrate the maximal blood plasma concentrations of
16 doxycycline that is achieved with the 40-milligram dose.

17 Q. Let's now look at example three of the Amin patents.

18 Can you please describe the tests done in
19 example 3?

20 A. Example 3 from the Amin patents are in vitro studies.
21 These are studies that used a murine macrophage cell line.
22 These were also cultured and treated with 5 to 80 micrograms
23 per milliliter of doxycycline and minocycline.

24 Measurements were taken at 14 and 20 hours.

25 Again, the substance measured was nitrite as an indicator of

Robbins - direct

1 nitric oxide production.

2 The results were displayed in figures 2A and 2B
3 from the Amin patent.

4 Q. Will you please describe the results as illustrated
5 in figures 2A and 2B?

6 A. These panels are similar to the previous ones we've
7 shown, with nitrite release being on the vertical axis in
8 the amount of doxycycline or minocycline on the horizontal
9 axis.

10 The panel on the left is at 14 hours. The panel
11 on the right is at 20 hours. Again, doxycycline is
12 represented by the triangles and minocycline by the squares
13 in each panel.

14 As we can see, there's --

15 Q. Did you mean the circles?

16 A. Yes. What did I say?

17 Q. Squares, I think.

18 A. Oh, I'm sorry. I use squares, but it's their slide.
19 Again, it shows a dose dependent decrease in the amount of
20 nitrite that is released.

21 Q. What concentrations of doxycycline had the effect of
22 reducing nitrite?

23 A. It appears from the slides, from the means and the
24 standard deviation bars which are given on each of the
25 triangles or circles, that it takes at least ten micrograms

Robbins - direct

1 per milliliter to cause a decrease in the amount of nitrite
2 release.

3 Now, let's take panel 2A, or 2A on the right,
4 the figure 2A. It does show that there is a reduction in
5 the amount of nitrite released, but if you look at the
6 standard, or standard deviation bars, you can see that
7 they're overlapping, indicating that there's likely no
8 significant difference between that dose of doxycycline and
9 the control.

10 Q. Where would the concentration of .6 micrograms per
11 milliliter show up in figures 2A and 2B?

12 A. It would show up far to the left, and I prepared a
13 slide which illustrates that, I believe. Yes. This is
14 example 3 from the Amin patents. Again, with the nitrite
15 again being on the vertical axis and the amount of
16 doxycycline or minocycline on the horizontal axis. We've
17 added the concentration that is present in the plasma
18 maximally after a 40-milligram dose, which is 0.6 micrograms
19 per milliliter. One can see that it is far to the left-
20 hand portion of this slide.

21 Q. How do the results illustrated in figures 1A, B and
22 C, as well as figures 2A and 2B relate to your first opinion
23 that 40 milligrams of doxycycline does not infringe the Amin
24 patent claims?

25 A. Well, there is no evidence that a 40-milligram dosage

Robbins - direct

1 actually decreases nitric oxide, but that hasn't been
2 directly tested, so my best next thing to go to was to look
3 at the in vitro data. And from this, we can see that the
4 maximal blood plasma concentrations are far below that what
5 I would expect to decrease the nitric oxide production from
6 these in vitro cells.

7 Q. You referred earlier in your description of your
8 background to some research that you have been involved
9 in.

10 What research have you personally been involved
11 in relating to doxycycline's effect on nitric oxide levels?

12 A. We've actually done some similar experiments to Amin,
13 but with a different cell line and with slightly different
14 measurements.

15 Q. Was that research performed for purposes of this
16 lawsuit?

17 A. It was not.

18 Q. When was that performed?

19 A. It was performed in -- well, it was published in
20 2005. It was probably performed earlier than that, probably
21 2003, 2004.

22 Q. Okay. Which publication describes this research?

23 A. That's the article in The Journal of Immunology,
24 first authored by Jeff Hoyt.

25 Q. Can you describe for us the research that you've

Robbins - direct

1 conducted?

2 A. Yes. The first point gives -- first bullet gives the
3 relevant reference, which is doxycycline modulates nitric
4 oxide production in murine lung epithelial cells.

5 Now, this is an in vitro study again on the
6 effect of doxycycline on nitrite production, NO production
7 and iNOS expression in murine lung alveolar epithelial
8 cells.

9 Doxycycline caused a dose-dependent decrease
10 in nitric oxide, nitrite and iNOS expression at higher
11 doses.

12 At a concentration of 30 micrograms per
13 milliliter, doxycycline showed an inhibition of iNOS protein
14 expression, nitrite, and actually nitric oxide concentration
15 in the head space above the culture supernatant. However,
16 there was no inhibition of nitrite concentration in order to
17 compare it with Amin patents at 10, 3, or .3 micrograms per
18 milliliter.

19 MR. REED: Your Honor, I offer DTX-1627.

20 MS. WILLGOOS: No objection, your Honor.

21 THE COURT: No objection? It's admitted.

22 BY MR. REED:

23 Q. Dr. Robbins, how does your own research relate to
24 your opinion in this case about whether the administration
25 of a 40-milligram daily dose of doxycycline decreases nitric

Robbins - direct

1 oxide production and inhibits iNOS expression?

2 A. Our data is fairly similar to the Amin patent data,
3 especially considering different cell lines, different
4 laboratories, et cetera. However, it does suggest like the
5 Amin patents that the maximal plasma concentration obtained
6 with the 40-milligram-per-day dosage of doxycycline is
7 likely insufficient to cause inhibition of iNOS expression
8 and nitric oxide production.

9 Q. We will get to your opinion about there being no
10 evidence of a link between rosacea and iNOS and nitric oxide
11 in a minute, but I'd like to ask you to assume for a minute
12 that Dr. Grisham's theory about the mechanism of action with
13 inducible nitrous oxide in rosacea is correct.

14 If his theory were correct, what evidence is
15 there that his proposed mechanism of action takes place at a
16 level of doxycycline achieved by the administration of
17 40 milligrams daily of doxycycline?

18 A. Well, assuming that his proposed mechanism of action
19 is correct, and there does not seem to be any evidence for
20 that, but assuming that's correct, it would mean that the
21 amount of doxycycline, at least present in the plasma, would
22 be insufficient to inhibit nitric oxide production and iNOS
23 expression in the tissues.

24 Q. Now, you know Dr. Grisham personally, don't you?

25 A. Oh, yes. Well.

Robbins - direct

1 Q. How do you know him?

2 A. Well, Matt and I were at the same institution. He
3 was in physiology and I also had an adjunct appointment in
4 the department of physiology. We're also collaborators,
5 easy for me to say, both in the lab, and wrote a number of
6 papers together.

7 Q. I take it you respectfully disagree with his opinion
8 about mechanism of action?

9 A. I think Matt is a wonderful guy and a wonderful
10 scientist, but I have to disagree with his opinion.

11 Q. Let's move to the second of your opinions, the one
12 that relates most closely to his opinions.

13 What is the second opinion you formed?

14 A. That Mylan does not infringe the Amin patents because
15 there is no evidence of a link between nitric oxide
16 production and/or iNOS expression and the papules and
17 pustules in rosacea.

18 Q. Do the Amin patents disclose or mention any causal
19 link between increased nitric oxide production and iNOS
20 expression?

21 A. They do not.

22 Q. And the papules and pustules of rosacea?

23 A. They do not.

24 Q. Is rosacea mentioned anywhere in the Amin patents?

25 A. I could not find rosacea mentioned in the patents.

Robbins - direct

1 Q. You went looking?

2 A. I went looking.

3 Q. Did you find any other diseases?

4 A. Oh, I found many other diseases.

5 Q. Can you give us a few examples?

6 A. These are some of the conditions recited by the Amin
7 patents. These include malaria, senescence, diabetes,
8 vascular stroke, neurodegenerative disorders, cardiac
9 disease and juvenile diabetes.

10 Q. Are there more?

11 A. There are more. This follows that, and this is
12 inflammatory conditions treatable by means of the present
13 invention that are mentioned, including osteoarthritis,
14 rheumatoid arthritis, acute and chronic infections, acute
15 and chronic bronchitis, sinusitis, et cetera, including drug
16 reactions, insect bites, burns, such as thermal, chemical,
17 electrical, and sunburn.

18 Q. That's quite a bit of conditions. Is rosacea
19 mentioned in this lengthy list of inflammatory conditions?

20 A. It is not.

21 Q. Why do you think rosacea is not included in the list?

22 A. I think because there's no evidence that nitric oxide
23 is involved in the pathogenesis of rosacea.

24 Q. Will you please tell us a little bit about what is
25 known about rosacea?

Robbins - direct

1 A. I am not a dermatologist, but given that caveat, I
2 did go to medical school and I do see a few people with
3 rosacea.

4 It is a common skin disorder with many
5 different clinical features. I agree with the previous
6 witnesses that thought that this was an unknown cause, and
7 there are a number of hypotheses that have been advanced
8 regarding the pathogenesis or the cause of rosacea.
9 However, none at the present time are sufficiently supported
10 by data to say that there's definitive cause.

11 Some indications seem for the pathogenesis of
12 rosacea. There's high levels of a protein called
13 cathelicidin. There's increased serine protease activity.
14 There's elevated expression of vascular endothelial growth
15 factors, such as VEGF, CD31, and lymphatic endothelium
16 marker DD240 and higher reactive oxygen species levels.

17 There have been a number of inflammatory
18 mediators involved proposed to be involved in the
19 pathogenesis, including Substance P, histamine, serotonin,
20 Bradykinin and prostaglandins, to mention a few.

21 Q. Now, you referred to testimony that you had heard.
22 You were in the courtroom when Dr. Webster testified?

23 A. I was.

24 Q. And you heard him testify that we still don't know
25 convincingly what the cause of rosacea is?

Robbins - direct

1 A. I did.

2 Q. And do you agree with his opinion?

3 A. Yes, I do.

4 Q. Similarly, were you in the courtroom when the
5 deposition testimony of Robert Ashley was played?

6 A. I was.

7 Q. And did you hear him testify that he didn't think the
8 causality of rosacea has ever been proven?

9 A. I did.

10 Q. Do you agree with that?

11 A. Yes.

12 Q. In the literature, is nitric oxide included in a list
13 of causes of rosacea?

14 A. There are a few papers mentioning nitric oxide, but
15 these are all review papers that list several causes or
16 hypotheses for rosacea.

17 Q. Did you review the articles relied upon by Dr.
18 Grisham as support for his opinion that there is this link?

19 A. I did.

20 Q. In your opinion, do those articles demonstrate that
21 nitric oxide or inducible nitric oxide synthase expression
22 is associated with rosacea?

23 A. In my opinion, they do not.

24 Q. Did you pick three of the articles that he relied on
25 to discuss today?

Robbins - direct

1 A. I did. I picked the three that I thought expressed
2 the best evidence for nitric oxide production.

3 Q. What can you tell us about these three articles?

4 A. All three of these articles, the Yamasaki and Gallo
5 and Korting and Schollmann and Bruch-Gerharz papers, several
6 of which have been mentioned previously, are review
7 articles.

8 And what a review article is, when you
9 write about the pathogenesis, treatment, clinical
10 recognition, et cetera, of a disease, and one of the things
11 that is commonly done is to discuss the possible hypothesis
12 regarding the pathogenesis. You especially want to
13 emphasize any new literature or new thoughts regarding the
14 disease.

15 Q. In review articles, what data is presented?

16 A. Usually data is not presented by the authors of the
17 article, but they reviewed the data from others.

18 Q. Okay. Let's look at each of these three articles in
19 turn.

20 First of all, what can you tell us about the
21 Yamasaki and Gallo review article?

22 A. Well, the Yamasaki and Gallo article didn't produce
23 any new data. What they did is they quoted an article by
24 Gurer to support their contention that nitric oxide might be
25 involved in the pathogenesis of rosacea.

Robbins - direct

1 MR. REED: Your Honor, I believe that the
2 plaintiffs had an objection to this slide, among others, and
3 I want to clarify the distinction we're making between the
4 levels of bullet points here.

5 BY MR. REED:

6 Q. You understand that plaintiff's expert, Dr. Grisham,
7 relied on the furthest left bullet points; is that right?

8 A. That's correct.

9 Q. And on this slide we see an indented bullet point
10 citing Gurer. Did Dr. Grisham cite to Gurer?

11 A. I'm not sure. I don't think so, but it is cited in
12 the article he cited as the reason for them making a
13 statement about nitric oxide.

14 Q. And let's take a look at what Yamasaki and Gallo said
15 about that.

16 A. Well, Yamasaki and Gallo say that rosacea individuals
17 showed higher reactive oxygen species, including nitric
18 oxide in plasma than controls.

19 Q. And then what does 68 and 75 mean at the end of that
20 sentence?

21 A. One of these is an article that has nothing to do
22 with rosacea, and the other is an article that we previously
23 mentioned from Gurer.

24 Q. So the two numbers are two footnotes rather than
25 references?

Robbins - direct

1 A. Yes.

2 Q. Okay. Did you look at the Gurer article?

3 A. I did.

4 MR. REED: Your Honor, I offer DTX-2180.

5 MS. WILLGOOS: Your Honor, I submitted my
6 objection to that exhibit this morning regarding that it was
7 not identified in this 282 notice. Other than that, I will
8 reserve that objection.

9 THE COURT: That's fine. It's admitted.

10 MR. REED: I'm a little confused because we're
11 not relying on this for invalidity.

12 THE COURT: The document is admitted. My ruling
13 from this morning.

14 MR. REED: Thank you.

15 (DTX-2180 was admitted into evidence.)

16 BY MR. REED:

17 Q. In reviewing Gurer, what did you find it said about
18 the nitric oxide, the implications of nitric oxide in
19 rosacea?

20 A. I actually found that it said something quite
21 different than quoted in the Yamasaki and Gallo paper. It
22 actually says that there is no statistically significant
23 difference found between the nitrate levels of the two
24 groups, referring to the patients with the rosacea in
25 control. The actual numbers are given here with the

Robbins - direct

1 standard deviation.

2 Furthermore, they go on to say at the end of the
3 article that the inflammatory species nitric oxide has no
4 role in the inflammatory mechanism of acne rosacea based on
5 this data.

6 Q. In other words, the article Yamasaki and Gallow did
7 not have any data to support their association between
8 nitric oxide and rosacea?

9 A. Yes. The article they cited actually implies that
10 nitric oxide was not involved.

11 Q. Okay. Let's now consider the next of the plaintiff's
12 articles, the Korting and Schollmann articles. Is this also
13 a review article?

14 A. This is also a review article.

15 Q. And does it purport to link rosacea with nitric
16 oxide?

17 A. It does.

18 Q. Is there any support for that connection?

19 A. There is not.

20 Q. What do Korting and Schollmann cite?

21 A. They cite two references. One by Golub, which
22 actually discusses osteoarthritis, and one by
23 Romero-Graillet, which actually discusses UV radiation or
24 sunburn and neither of which discuss rosacea.

25 MR. REED: Your Honor, I offer DTX-1065 and

Robbins - direct

1 DTX-1872.

2 MS. WILGOOS: Your Honor, with our prior
3 objection this morning, we have no further objection.

4 THE COURT: They are admitted.

5 (DTX-1872 and DTX-1065 received into evidence.)

6 BY MR. REED:

7 Q. So the Golub and Romero-Graillet articles, what do
8 they say about rosacea?

9 A. They don't say anything about rosacea. They do
10 discuss nitric oxide.

11 Q. Let's turn then to the third of the articles that
12 Dr. Grisham relayed on the Bruch-Gerharz art. What can you
13 tell us about that?

14 A. Well, Bruch-Gerharz is another review article which
15 does also have no original data but does cite others in the
16 literature.

17 Q. Are the four articles that it cites listed in the
18 supplemental bullet points here?

19 A. Yes, there are four. I'll go through the first three
20 relatively quickly. The Deliconstantinos article deals with
21 UV radiation and sunburn.

22 The second article by Goldsmith is also UV
23 radiation or sunburn.

24 The third article by Hayes discusses dithranol
25 induced chemical burn to the skin. And,

Robbins - direct

1 The four by Sauermann requires more explanation.

2 MR. REED: Before we go that there, I offer

3 DTX-1527, also 1597, also 1620, and 1879.

4 MS. WILGOOS: Subject to our objections this

5 morning, we have no further objection.

6 THE COURT: They are admitted.

7 (DTX-1527, DTX-1597, DTX-1620, DTX-1879 received

8 into evidence.)

9 BY MR. REED:

10 Q. Dr. Robbins, please describe for us what you saw when

11 you reviewed Sauermann, et al?

12 A. Sauermann actually reported an abstract, I believe

13 the year was 1997, that a nonspecific nitric oxide synthase

14 inhibitor, that which inhibits both the constitutive nitric

15 oxide and the inducible nitric oxide synthase showed

16 improvement of chemical induced erythema on the forearm.

17 The article goes on to say that Sauermann

18 treated patients with grade 1 rosacea. However, there were

19 only four rosacea patients treated with this nonspecific

20 nitric oxide inhibitor.

21 My understanding is that grade one patients do

22 not have the papules and pustules of rosacea and that is

23 limited to erythema only. There are several problems with

24 Sauermann's abstract.

25 First, there was no controls in place, and

Robbins - direct

1 Sauermann's brief conclusions of significant improvement in
2 these rosacea patients failed to state improvement was due
3 to inducible nitric oxide synthase inhibition as opposed to
4 cNOS inhibition or even for what they understand the
5 improvement was.

6 Sauermann failed to elaborate on the study
7 methodology or symptoms of these patients.

8 I think it's somewhat telling to date that these
9 studies have not been published in a full length manuscript
10 despite many years that have passed since publication of
11 this abstract.

12 Q. In short, could you reasonably conclude that
13 Sauermann treated the papules and pustules of the four
14 rosacea patients by inhibiting iNOS?

15 A. Not based on the data presented on the abstract.

16 Q. So which of the cited references actually report a
17 link between nitric oxide produced by iNOS and the papules
18 and pustules of rosacea?

19 A. In my opinion, none of the articles actually support
20 that link.

21 Q. Can you describe the conclusions you came to after
22 reviewing the references cited by Dr. Grisham?

23 A. I conclude that there is no published article
24 contains data demonstrating that the papules and pustules
25 of rosacea are caused by increased expression of inducible

Robbins - direct

1 nitric oxide synthase or nitric oxide production.

2 There is no published article that contains data
3 demonstrating that there is any link between endogenous
4 nitric oxide production and the papules and pustules of
5 rosacea.

6 Q. Now, let's move on to the third of your opinions.
7 This one doesn't relate to invalidity.

8 What opinion have you formed regarding inherent
9 anticipation?

10 A. The prior art in August 1996 inherently anticipates
11 the Amin patents, which merely recognize the inherent
12 property of a tetracycline to decrease nitric oxide
13 production and inhibit iNOS expression.

14 Q. What did you find in the Amin patents themselves
15 about how the inventors characterized what they purported to
16 invent?

17 A. Well, the inventor -- the Amin patents themselves
18 also may indicate that nothing is novel. They use the term
19 "observation" in the '395 patent.

20 Q. How about in the file history?

21 A. And in the file history, they used the term
22 "recognition" by the investigators.

23 Q. Now, in the Amin patents, what do they say about the
24 prior understanding of the relationship between nitric oxide
25 and iNOS and inflammatory conditions?

Robbins - direct

1 A. They list a number of acknowledgment, a prior
2 understanding of nitric oxide and inducible nitric oxide
3 synthase in a number of inflammatory conditions. However,
4 of the conditions that are being talked about, one of which
5 is rheumatoid arthritis, they also talked about
6 osteoarthritis in this context, and another that they have
7 talked about or will talk about is periodontitis.

8 Q. I don't think periodontitis appears in the patent.

9 A. You're correct.

10 Q. Prior to 1996, August of 1996, was periodontitis a
11 chronic inflammatory condition that was known to be related
12 to nitric oxide and inducible nitric oxide synthase?

13 A. It was.

14 Q. Let's talk first about rheumatoid arthritis. What
15 did you find in the literature regarding rheumatoid
16 arthritis that was known prior to August of 1996?

17 A. Well, consistent with the Amin patents, numerous
18 articles showed that rheumatoid arthritis was known to
19 involve nitric oxide and/or inducible nitric oxide synthase.
20 The dates of the articles show this involvement and was
21 understood before the filing of the Amin patents.

22 I have listed some of those articles here,
23 including Farrell, which was published in 1992:

24 Amin himself in 1995.

25 Sakurai in '95.

Robbins - direct

1 Clancy in 1995.

2 A Wahl patent. And,

3 Murrell in 1996. The Wahl patent in 1995.

4 MR. REED: Your Honor, I offer DTX numbers 1555,
5 also 1345, also 1876, also 1462, also 2012, and 1765.

6 (DTX Nos. 1555, 1345, 1876, 1462, 2012, 1765
7 received into evidence.)

8 MS. WILGOOS: Reserving our objections from this
9 morning, we have no further objections, your Honor.

10 THE COURT: They are admitted.

11 MR. REED: Thank you.

12 BY MR. REED:

13 Q. Now, the other condition you mentioned was
14 periodontitis. Can you please explain what you found
15 regarding periodontitis that was known prior to August 1996?

16 A. Like rheumatoid arthritis, numerous articles show
17 that periodontitis was known to involve nitric oxide and
18 inducible nitric oxide synthase.

19 Dates of the articles show this involvement was
20 understood before the filing of the Amin patents.

21 We list three here, including Wahl 1994, Wahl
22 again in the patent in 1995, and Murrell, et al in 1996.

23 Q. Prior to August of 1996, what had been disclosed
24 about administering low doses of tetracyclines to patients
25 with rheumatoid arthritis and periodontitis?

Robbins - direct

1 A. There are some references regarding administering low
2 dose that is 20 milligrams twice per day of doxycycline to
3 rheumatoid arthritis and periodontitis patients.

4 Here are four references. The first is by
5 Golub, et al who gave 20 milligrams of doxycycline twice
6 daily to periodontitis patients. This is published in 1990.

7 Another article by Bouwsma, et al gave
8 20 milligrams twice daily and 20 milligrams once daily to
9 periodontitis patients. This was published in 1992.

10 Schroeder, et al gave 20 milligrams twice daily
11 to periodontitis patients, published as an extract in 1992.

12 And Greenwald, et al, gave 20 milligrams twice
13 daily to rheumatoid arthritis patients in 1994.

14 MR. REED: Your Honor, I offer Exhibits
15 DTX-2183, also 2181, also 2182, and 2184.

16 MS. WILGOOS: No objection, your Honor.

17 THE COURT: They're admitted.

18 (DTX Nos. 2182, 2182, 2183, 2184 received into
19 evidence.)

20 MR. REED: And I believe I forget to move for
21 the admission of DTX-1162, also 2012, and 2074.

22 MS. WILGOOS: Subject to our objections this
23 morning, we have no further objections, your Honor.

24 THE COURT: They are admitted.

25 (DTX Nos. 1162, 2012, 2074 received into evidence.)

Robbins - direct

1 BY MR. REED:

2 Q. Returning now to these low dose administrations of
3 doxycycline. What do you know about the maximum steady
4 state blood plasma concentration of doxycycline achieved by
5 a dosage of 20 milligrams twice daily?

6 A. The maximum steady state dosage of doxycycline
7 administered 20 milligrams twice per day approximate that
8 of the 40 milligrams once a day formulation and is
9 approximately 0.8 micrograms per mil as I recall in the
10 literature.

11 Q. Is the Periostat package insert what you looked at?

12 A. It is. And here is the data from that, giving the
13 steady state levels at 20 milligrams twice per day as 790
14 plus or minus 285 nanograms per mil or approximately
15 .8 micrograms per mil.

16 Q. And you mentioned the Cmax of Oracea as well?

17 A. I did.

18 Q. And where did you find that Cmax?

19 A. And this is taken from the Oracea package insert, and
20 it is 600, plus or minus 194, or .6 micrograms per
21 milliliter.

22 Q. Now, what would be the difference in terms of any
23 affect on the levels of nitric oxide and iNOS expression
24 between a once-a-day 40 milligram administration on the one
25 hand and a twice-a-day 20 milligram administration, on the

Robbins - direct

1 other hand, of doxycycline?

2 A. Looking at the Cmax levels, I do not believe that
3 those two numbers are very likely to be statistically
4 significantly different since the standard deviations
5 appear to overlap. It is difficult for me, having run dose
6 response curves with this and seen the dose response curves
7 with the patents and in the literature that there would be
8 any biological difference between these concentrations.

9 Q. Now, just to be clear, you told us that your opinion
10 is that there is no evidence that 40 milligrams administered
11 once daily of doxycycline would decrease endogenous nitric
12 oxide production or inhibit iNOS expression; right?

13 A. That's true.

14 Q. But for the sake of argument, if 40 milligrams of
15 doxycycline once a day is sufficient to decrease
16 endogenously produced nitric oxide and inhibit iNOS
17 expression as plaintiffs contend, then what effect would
18 20 milligrams of doxycycline administered twice per day
19 have?

20 A. I would suspect that it would have no different
21 effect compared to the 40 milligrams once a day based on the
22 Cmax concentrations.

23 Q. And, again, I understand that you don't agree with
24 this theory, but if it were true, when did it start to
25 exist?

Robbins - direct

1 A. If it were true, and it is true, that doxycycline
2 will inhibit nitric oxide and inducible nitric oxide
3 synthase expression in sufficient concentrations, but if it
4 is true that doxycycline that was used in these patents is
5 the same as the doxycycline I used in my experiments and was
6 the same doxycycline that was used prior to 1996, it is the
7 same doxycycline, the same molecule.

8 Q. So who are you aware of that was administering doses
9 of doxycycline to patients with chronic inflammatory
10 conditions characterized by increased NO production or iNOS
11 expression prior to August of 1996?

12 A. The four prior references that I gave previously all
13 indicate that 20 milligrams twice per day were given to
14 rheumatoid arthritis and periodontitis patients.

15 If doxycycline were to inhibit nitric oxide and
16 inducible nitric oxide synthase, and I don't agree that
17 there is evidence to support that, then each of these would
18 have inhibited nitric oxide and inducible nitric oxide
19 synthase. All are published prior to 1996.

20 Q. Now, none of these four prior art references here
21 that you say were administering 20 milligrams of doxycycline
22 twice daily prior to August of 1996 mention nitric oxide or
23 inducible nitric oxide synthase; is that right?

24 A. That is true.

25 Q. Does that matter to your opinion?

Robbins - direct

1 A. It does not because the inhibition is an inherent
2 property of the molecule and these diseases are all known to
3 be associated with increased nitric oxide production and
4 inducible nitric oxide synthase expression.

5 Q. Okay. Let's go now to the claims of the Amin patent.
6 And I would like you to please explain your opinion that the
7 asserted Amin patent claims are anticipated starting first
8 with the '395 patent, claim 1.

9 A. Well, this claim says that, this is a method for
10 inhibiting nitric oxide production in a mammal system,
11 comprising providing to the mammalian system an amount of a
12 tetracycline compound sufficient to cause a disease in the
13 amount of nitric oxide produced endogenously by the
14 mammalian-system.

15 Q. And how did the prior art references that you
16 identified previously anticipate this claim?

17 A. Each of the prior art references would appear to
18 anticipate this claim because assuming the low doses of
19 doxycycline inhibit nitric oxide and iNOS, that means a
20 mammalian system, in this case, humans, were being treated
21 with these compounds prior to 1996 -- the filing of the
22 patent in August of 1996.

23 Q. Can you please explain your anticipation opinion with
24 respect to claim 2?

25 A. In claim 2, it says the method according to claim 1,

Robbins - direct

1 wherein the tetracycline compound has substantially no
2 antimicrobial activity in the mammalian system.

3 Q. And what do you understand the plaintiffs contend
4 with respect to whether the 40 milligram daily dose of
5 doxycycline in Oracea has antimicrobial activity?

6 A. My understanding is that the plaintiffs contend that
7 there is no antimicrobial activity in 40 milligrams, once
8 daily, of the Oracea product and the proposed Mylan product.

9 Q. You don't have an opinion on whether that is true or
10 not; correct?

11 A. Well, I'm very confused after hearing the discussions
12 today, but I do not.

13 Q. Assuming that plaintiffs are correct about that
14 antimicrobial activity, at that dosage level, what is your
15 opinion regarding claim 2 in light of the four references
16 that you mentioned earlier?

17 A. Well, assuming that is correct, that would mean that
18 the doxycycline used in filing the patent in 1996 is the
19 same doxycycline that was used in the prior art references.
20 Therefore, it would have the same effect in before 1996 as
21 it did in 1996 because the molecule itself hadn't changed.

22 Q. So it's your opinion that claim 2 is anticipated?

23 A. Yes, it is.

24 Q. How about claim 4?

25 A. Claim 4 states that the method to claim 1 involves an

Robbins - direct

1 tetracycline compound, and a number which are listed,
2 including doxycycline.

3 Q. And what does that mean about the prior art?

4 A. In the prior art references, all of them use
5 doxycycline, which is listed in claim 4.

6 Q. And in conclusion, what is your opinion about claim
7 4?

8 A. That, therefore, the prior art references anticipate
9 claim 4, but because they used doxycycline.

10 Q. How about claim 11 of the '395 patent?

11 A. Claim 11 states it's a method of treating a mammal
12 having a medical condition characterized by excess
13 endogenous production of nitric oxide, comprising
14 administering to the mammal an amount of a tetracycline
15 compound sufficient to inhibit endogenous nitric oxide
16 production in the mammal.

17 Q. I don't mean to cut you off.

18 A. The prior art references --

19 Q. Please continue.

20 A. The prior art references would all seem to have
21 anticipated this because the amount of the doxycycline being
22 given, if it was sufficient to inhibit nitric oxide, would
23 be the same in the prior art references as it was when the
24 patent was filed in August of 1996.

25 Q. I'm going to suggest that we probably don't need you

Robbins - direct

1 to read the language of each and every claim since we have a
2 number of other claims to go through.

3 A. I'm sorry. I'm just doing it to refresh my memory to
4 make sure I don't misspeak.

5 Q. With respect to claim 13, will you please explain
6 your anticipation opinion?

7 A. In claim 13, it stipulates that these are a medical
8 condition that is a chronic inflammatory condition. The
9 prior art references deal with rheumatoid arthritis and
10 periodontitis, which are chronic inflammatory conditions.

11 Q. Just for the sake of clarity, you were talking about
12 the four prior art references that talked about
13 administering 20-milligram doses twice daily?

14 A. Yes. To rheumatoid arthritis and periodontitis
15 patients.

16 Q. Thank you.

17 Would you explain your opinion with regard
18 to claim 14?

19 A. I'm sorry?

20 Q. Will you please explain your anticipation opinion
21 with respect to claim 14?

22 A. Oh, claim 14. I'm sorry. I didn't see it change. I
23 thought we were still on 11.

24 That the method according to claim 11 wherein
25 the tetracycline compound has substantially no

Robbins - direct

1 anti-microbial activity.

2 Again, it is unclear to mean what
3 anti-microbial activity is. I have no opinion. But
4 assuming that's true, as the plaintiffs contend, then the
5 doxycycline administered or proposed in the patent would be
6 the same as it was in the prior art references at
7 20 milligrams twice a day.

8 Q. Those four references?

9 A. The four references. What did I say? Two?

10 Q. No. You didn't say a number.

11 A. Okay. Four references.

12 Q. Can you describe your anticipation opinion with
13 respect to claim 16 of the '395 patent?

14 A. This is similar to what we mentioned before, where
15 they stipulate that this is the tetracycline compound.
16 Again, doxycycline is limited -- is listed there, and each
17 of these four prior art references use doxycycline.

18 Q. And is your opinion that each of those anticipates
19 claim 16 of the '395 patent?

20 A. Because they are using doxycycline, yes.

21 Q. Would you please describe your anticipation opinion
22 with respect to claim 1 of the '775 patent?

23 A. Claim 1 of the '775 patent is very similar to claim 1
24 of the '395 patent except it mentions inducible full nitric
25 oxide synthase. From my standpoint, this is very, very

Robbins - direct

1 similar to what I said previously, applies to this. That
2 these diseases are associated with inducible nitric oxide
3 synthase, and therefore treating these with 20 milligrams
4 twice a day would anticipate this claim.

5 Q. Which diseases?

6 A. Rheumatoid arthritis and periodontitis.

7 Q. Thank you.

8 Please describe your anticipation opinion
9 with respect to claim 2.

10 A. Again, it mentions no anti-microbial activity. If
11 the plaintiffs contend there is no anti-microbial activity
12 with the 40-milligrams-a-day dosage, it would be anticipated
13 that the 20 milligrams twice a day used to treat these
14 rheumatoid arthritis patients and periodontitis patients
15 would show no anti-microbial activity as well, and,
16 therefore, it anticipates this claim.

17 Q. Please describe your anticipation opinion with
18 respect to claim 4.

19 A. Again, this lists the various tetracycline compounds,
20 one of which is doxycycline, which was used in the four
21 prior art references to treat rheumatoid arthritis and
22 periodontitis, and then for this would be anticipated by the
23 four prior art references.

24 Q. For all the same reasons you described before?

25 A. All the same reasons I described before.

Robbins - direct

1 Q. Will you please describe your anticipation opinion
2 with respect to claim 5?

3 A. Again, this mentions a method -- a condition
4 characterized by increased nitric oxide production, and all
5 the prior art references are -- deal with rheumatoid
6 arthritis or periodontitis, two conditions associated with
7 increased nitric oxide production.

8 Q. And what did you conclude from that?

9 A. I conclude that these four prior art references
10 anticipate this claim.

11 Q. Will you please explain your anticipation opinion
12 with respect to claim 9 of the '775 patent?

13 A. This is similar to the ones before except mentioning
14 the activity of inducible nitric oxide synthase.

15 It's my opinion that the four prior art
16 references anticipate this claim because each has been
17 associated with increased inducible nitric oxide synthase.

18 Q. In sum, is it your opinion that the four prior art
19 references which describe treating periodontitis and
20 rheumatoid arthritis with 20 milligrams of doxycycline twice
21 a day anticipate each and every one of the asserted claims
22 of the Amin patents?

23 A. It is.

24 Q. Thank you.

25 Let's talk now about higher dosages of

Robbins - direct

1 tetracyclines.

2 Prior to August of 1996, were rheumatoid
3 arthritis and periodontitis sometimes treated with doses of
4 tetracyclines greater than 20 milligrams twice daily?

5 A. Yes, they were. We're calling the arbitrary number
6 of tetracyclines 50 milligrams twice per day or greater to
7 rheumatoid arthritis and periodontitis.

8 I've listed a number of references here.
9 These include references by Golub, 200 milligrams of
10 minocycline per day to periodontitis patients.

11 Greenwald, a hundred milligrams of
12 minocycline twice a day to rheumatoid arthritis patients.

13 Golub again, 30 milligrams doxycycline twice
14 per day to periodontitis patients.

15 Golub again, a hundred milligrams
16 doxycycline per day to periodontitis patients.

17 And Tilley, 100 milligrams twice per day to
18 rheumatoid arthritis patients. That was minocycline.

19 MR. REED: Your Honor, I offer Exhibits
20 DTX-2188, also 2186, also 2183, also 1603, and 2187.

21 MS. WILLGOOS: No objection, your Honor.

22 THE COURT: They are admitted.

23 (DTX-2188, 2186, 2183, 1603 and 2187 were
24 admitted into evidence.)

25 BY MR. REED:

Robbins - direct

1 Q. In your opinion, can you summarize for us your
2 opinion with respect to these five prior art references and
3 all the asserted claims of the Chang patents? Sorry. The
4 Amin patents.

5 A. Well, the Amin patents are anticipated because,
6 again, tetracyclines, this time in higher doses, were used
7 to treat each of these conditions, which are known to be
8 chronic inflammatory conditions associated with increased
9 nitric oxide production and increased inducible nitric oxide
10 synthase expression.

11 Q. What do you know from your own research about
12 administering higher doses of tetracyclines?

13 A. I know from my own research that at least higher
14 concentrations in vitro will inhibit inducible nitric oxide
15 synthase.

16 Q. What is one of ordinary skill in the art able to
17 learn from the publication regarding your research about
18 doxycycline's ability to inhibit the expression of iNOS and
19 decrease the production of endogenous nitric oxide?

20 A. Each of the prior art references, the data reported
21 in the Amin patents and my own research, all establish it
22 was an inherent property of doxycycline to inhibit inducible
23 nitric oxide of expression and the production of nitric
24 oxide.

25 The nitric oxide, the doxycycline used in

Robbins - direct

1 the patents is the same that I used, and it was the same
2 that was previously used. Perhaps a minor difference in the
3 salts, et cetera.

4 Q. With respect just to the publication regarding your
5 data, what would one of ordinary skill in the art be able to
6 learn from that publication about doxycycline's ability to
7 inhibit the expression of iNOS and decrease the production
8 of endogenous NO?

9 A. At high enough concentrations, doxycycline will
10 inhibit inducible nitric oxide and synthase and nitrous
11 oxide production. However, at lower dosages, it does not.

12 Q. I'm not sure if you described for us the summary of
13 your opinions that the Amin patents were inherently
14 anticipated completely or I cut you off.

15 Had you finished?

16 A. Yes. I think that these -- that the tetracyclines
17 that were used to treat the chronic inflammatory
18 conditions characterized by NO production or iNOS expression
19 were done long before August of 1996. And each of these
20 references, the data reported the Amin patents and my own
21 research all established it was an inherent property of
22 doxycycline to inhibit iNOS expression and production, et
23 al. Therefore, one of skill in the art would recognize that
24 this inherent property of tetracycline was necessarily
25 present in the prior art.

Robbins - direct

1 Q. Let's move now to your final opinion. Can you
2 describe for us what opinion you formed about whether the
3 Amin patents are enabled?

4 A. The Amin patents do not enable one of skill in the
5 art to determine a dose of tetracycline that with
6 substantially no antibiotic activity and it also decreases
7 NO production or inhibits iNOS expression.

8 Q. What are the three claims that are the focus of your
9 opinion on enablement?

10 A. The three claims are claim 2 and 14 from the '395
11 patent, and claim 2 from the '775 patent.

12 Q. What claim or claims of these are you focused on?

13 A. That these have substantially no anti-microbial
14 activity in each of these, and also have sufficient amounts
15 of doxycycline to inhibit nitric oxide production and iNOS
16 expression.

17 Q. You're familiar with the Court's ruling on claim
18 construction regarding that phrase?

19 A. Yes, I am.

20 Q. Can you tell us what you understand to be the
21 relevant portion of that claim construction for purposes of
22 your enablement opinion?

23 A. Well, there are two things that the Court's claim
24 construction states regarding the tetracycline compound.
25 The first is that it can be a compound that has been

Robbins - direct

1 modified chemically to reduce or laminated anti-microbial
2 activity, or that the tetracycline compound possesses
3 anti-bacterial activity, but is employed in an amount that
4 has substantially no antibacterial effect.

5 Q. And what of those is relevant here?

6 A. The second one is relevant.

7 Q. What do you understand is necessary to enable the
8 claims that are the focus of your enablement opinion, claim
9 2 and 14 on the '395 patent and claim 2 of the '775 patent?

10 A. That the patent should teach a dose that was
11 sufficient to inhibit nitric oxide and inducible nitric
12 oxide synthase expression, but was sufficiently low that it
13 had no, essentially no anti- -- substantial antibacterial
14 effect.

15 Q. What was the lowest tetracycline concentration for
16 which data from studies was disclosed in the Amin patents?

17 A. The lowest concentration of anti- -- of doxycycline
18 and minocycline used in those patents was five micrograms
19 per milliliter.

20 Q. Do the Amin patents teach that five micrograms per
21 milliliter of doxycycline is a concentration that has
22 substantially no anti-microbial activity?

23 A. They do not.

24 Q. How about the ability to inhibit iNOS expression?

25 A. They would seem to indicate that that concentration

Robbins - cross

1 from those in vitro studies is insufficient to inhibit iNOS
2 expression and nitric oxide production.

3 Q. Do the Amin patents provide any teaching or
4 description about an amount or dose of tetracycline that has
5 both substantially no anti-microbial activity and also at
6 the same time decreases nitric oxide production and/or
7 inhibits iNOS expression?

8 A. They do not.

9 MR. REED: No further questions, your Honor, at
10 this point.

11 THE COURT: All right. We'll have
12 cross-examination.

13 CROSS-EXAMINATION

14 BY MS. WILLGOOS:

15 Q. Good afternoon, Dr. Robbins.

16 A. Good afternoon.

17 Q. First, I want to ask you a clarifying question
18 because I'm a little bit confused by some of your opinions.

19 Have you actually formed an opinion regarding
20 whether or not iNOS is up-regulated in rosacea?

21 A. I have not actually formed an opinion. What I've
22 stated is that there's no evidence that iNOS is
23 up-regulated.

24 Q. Okay. Thank you for the clarification.

25 Now, were any of the experiments in the Amin

Robbins - cross

1 patents in vivo experiments?

2 A. They were not.

3 Q. Okay. So no blood serum concentrations of humans
4 were tested in the studies that were part of the Amin
5 patents; correct?

6 A. That is correct.

7 Q. Okay. Let's pull up DDX-414. Thank you.

8 Now, this graph, which is in the Amin patents,
9 the micrograms per milliliter on the X axis, that is not a
10 blood serum concentration; is that correct?

11 A. That is not.

12 Q. Okay. And, similarly, the other graphs in the Amin
13 patents do not contain any blood serum concentrations as
14 part of the graph?

15 A. That is correct.

16 Q. Thank you.

17 Now, let's discuss briefly the Gurer article
18 that you testified about. And I believe you testified that
19 in that article, they concluded that iNOS was not, there was
20 no nitric oxide production in rosacea. Is that what you
21 testified to?

22 A. That's correct.

23 Q. All right. In that article, other than the serum
24 levels of nitrate, there were no other indicators of nitric
25 oxide that were tested; is that correct?

Robbins - cross

1 A. I believe that is correct.

2 Q. Okay.

3 A. As I recall the paper.

4 Q. All right. And there were no skin biopsies, for
5 example?

6 A. There were no skin biopsies.

7 Q. Okay. Now, it's possible for local tissue to have an
8 increased NO production in iNOS expression without being
9 able to detect that in serum; is that correct?

10 A. That is correct.

11 Q. Okay. And, indeed, your own studies have shown that;
12 is that correct?

13 A. Yes. We have studies with lung disease that have
14 shown that. Correct.

15 Q. Okay. So this Gurer article is not sufficient to
16 show that iNOS or nitric oxide is in rosacea; correct?

17 A. No, it is not.

18 Q. You're a pulmonologist; correct?

19 A. That is true.

20 Q. And you agree that asthma is known to have an
21 up-regulation of iNOS activity?

22 A. I'm sorry?

23 Q. Is iNOS activity up-regulated in asthma?

24 A. Yes.

25 Q. Okay. As a clinical study, you could test different

Robbins - cross

1 doses of doxycycline in asthma patients and determine if
2 those dosages affected nitric oxide production secondary to
3 iNOS; right?

4 A. You could, yes.

5 Q. Okay. And if one was to do such an experiment in
6 humans, one would likely propose using a dose of such a
7 tetracycline that was already available and known to be
8 relatively safe; is that right?

9 A. Yes.

10 Q. And it would be reasonable that similar testing could
11 be done in other conditions? Other disease states?

12 A. Yes.

13 Q. Elevated nitric oxide levels are typically part of
14 the response to inflammatory stimuli; correct?

15 A. Elevation of nitric oxide production and nitric oxide
16 levels is seen in many inflammatory diseases, that's
17 correct.

18 Q. It's typically part of the response to inflammatory
19 stimuli; correct?

20 A. It is very often part of it, yes. Correct.

21 Q. Okay. Typically?

22 A. Typically.

23 Q. The production of large amounts of nitric oxide
24 associated with inflammatory responses generated by iNOS is
25 sometimes generated in quantities sufficient to be

Robbins - cross

1 cytotoxic; right?

2 A. State that one more time.

3 Q. Sure. The production of large amounts of nitric
4 oxide associated with inflammatory responses is generated by
5 iNOS in quantities sufficient to be cytotoxic right?

6 A. Yes, there is data that suggested that.

7 Q. And expression of the gene coding for iNOS and cells
8 in tissue involved in the inflammatory response leads to
9 increased nitric oxide levels; correct?

10 A. Yes.

11 Q. Okay. And the expression of iNOS resulting in
12 elevated nitric oxide levels is present in most inflammatory
13 diseases?

14 A. In most, yes. Probably, that's fair. Correct.

15 Q. And this increased nitric oxide production has
16 numerous downstream effects, including vasodilation,
17 increased microvascular permeability, altered white blood
18 cell function and tissue damage; correct?

19 A. That is correct.

20 Q. The classic hallmarks of that inflammation are
21 erythema, edema, and pain; correct?

22 A. That's correct.

23 Q. And you would also agree that the clinical symptoms
24 of rosacea include those classic signs of inflammation,
25 erythema, edema and sometimes pain; correct?

Robbins - cross

1 A. That's correct.

2 Q. And these classic hallmarks of inflammation are often
3 associated with the papules and pustules of rosacea;
4 correct?

5 A. Inflammation is part of rosacea, as are the papules
6 and pustules, yes. Correct.

7 Q. The clinical symptoms of rosacea include the classic
8 signs of inflammation which are associated with the papules
9 and pustules; is that correct?

10 A. That's correct.

11 Q. And pustules are small raised areas of the skin that
12 contain pus from white blood cells; is that right?

13 A. That's correct.

14 Q. And white blood cells are also called leukocytes;
15 correct?

16 A. Yes.

17 Q. And that includes both neutrophils and macrophages;
18 right?

19 A. Yes.

20 Q. Is it your understanding that the type of white blood
21 cell that is most characteristic of rosacea is the
22 neutrophil, also called a polymorphonuclear leukocyte?

23 A. Yes.

24 Q. Let's talk about the rosacea symptom of edema. Edema
25 is usually caused by leakiness of blood vessels with of

Robbins - cross

1 fluid and protein outside the vessel and into the tissue;
2 correct?

3 A. That is correct.

4 Q. Let's talk about erythema. That means redness,
5 right?

6 A. Erythema means redness.

7 Q. And at sites of inflammation, erythema is due to
8 dilatation of blood vessels; is that correct?

9 A. That is correct.

10 Q. Now, Dr. Robbins, is it your opinion that Oracea
11 is -- well, do you understand that Oracea is a 40 milligram
12 once-a-day treatment approved by the FDA to treat the
13 papules and pustules of rosacea?

14 A. Yes.

15 Q. Okay. And you believe it's effective for that
16 purpose; right?

17 A. I'm sorry.

18 Q. Do you believe it's effective for that purpose?

19 A. Yes.

20 Q. Are you an expert in periodontology or dentistry?

21 A. Certainly not.

22 Q. And you haven't treated a patient with periodontitis
23 or gum disease in the recent past; correct?

24 A. No.

25 Q. Would you agree that tetracyclines are usually used

Robbins - cross

1 as antimicrobial medications?

2 A. Yes.

3 Q. And that was true prior to August of 1996 as well?

4 A. That is true.

5 Q. Okay. I think you testified about this in your
6 direct but just for confirmation. You have not formed an
7 opinion as to whether or not 20 milligrams of doxycycline
8 administered twice a day is a sub-antibacterial amount?

9 A. That is correct.

10 Q. And you have never prescribed doxycycline
11 20 milligrams a day; correct?

12 A. I don't think so. Certainly not that I can recall.

13 Q. Okay. And are you aware that in August of 1996,
14 there was no 20 milligram doxycycline product that was
15 commercially available?

16 A. Yes.

17 Q. Now, you have not formed an opinion as to whether or
18 not 20 milligrams of doxycycline twice a day would be
19 effective to treat periodontitis, have you?

20 A. We gave prior art references where 20 milligrams was
21 given to periodontitis patients. I have not formed an
22 opinion whether those patients improved but there is data
23 that doxycycline does improve periodontitis.

24 Q. Okay. Have you formed an opinion as to whether or
25 not 20 milligrams of doxycycline twice a day would be

Robbins - cross

1 effective to treat periodontitis?

2 A. From the literature, I would have to say yes, it
3 would be.

4 Q. Do you recall me asking you that question at your
5 deposition?

6 A. I do not.

7 Q. Okay. Do you recall giving the response that you had
8 not formed an opinion on that matter?

9 A. I might have said that.

10 Q. Okay. So let's just try this again. You have not
11 formed an opinion regarding whether or not 20 milligrams of
12 doxycycline twice a day would be effective to treat
13 periodontitis; correct?

14 A. That's correct. It's really outside my area of
15 expertise.

16 Q. And you don't know what percentage of patients with
17 periodontitis in a clinical practice, if any, would have
18 increased nitric oxide production; correct?

19 A. Of what type of patients?

20 Q. Periodontitis patients.

21 A. I do not.

22 Q. And you don't have opinion as to whether or not
23 doxycycline decreases iNOS expression or NO production in
24 patients with periodontitis; correct?

25 A. The doxycycline increases it.

Robbins - cross

1 Q. You have not formed an opinion -- I'll just repeat
2 the question. You have not formed an opinion regarding
3 whether or not doxycycline decreases iNOS expression or NO
4 production in human patients with periodontitis; is that
5 correct?

6 A. Given that is outside my area of expertise, the
7 answer is no.

8 Q. Now, let's talk specifically about some of the
9 references that you cited in your direct.

10 The first one I'd like to discuss is the Bouwsma
11 abstract, which is at DTX-2181. And this abstract does not
12 discuss nitric oxide production; is that right?

13 A. That is correct.

14 Q. And --

15 A. Could you put it up, please, though? You must have
16 it, if you have got that.

17 Q. You also have it in your witness book, if you would
18 like.

19 A. Yes. What number is it again?

20 Q. DTX-2181.

21 A. Thank you.

22 Q. You're welcome.

23 A. Yes, I have it at the lower right-hand corner.

24 Q. There is no indication in this abstract of
25 measurements regarding nitric oxide or iNOS; correct?

Robbins - cross

1 A. There is not.

2 Q. Okay. And there is no mention in this article of NO
3 or iNOS at all; correct?

4 A. There is not.

5 Q. Let's turn to the next reference, the Schroeder
6 abstract, which is DTX-2182. And I believe that is also in
7 your book.

8 And the Schroeder abstract does not mention
9 nitric oxide and inducible nitric oxide synthase; correct?

10 A. No, it does not.

11 Q. Okay. And it also does not mention whether or not it
12 was determined if these patients had increased inducible
13 nitric oxide synthase over normal levels; correct?

14 A. No, it does not.

15 Q. Okay. And, similarly, there is no evidence in this
16 abstract that after administration of the drug, patients
17 were later tested to determine whether inducible nitric
18 oxide synthase was decreased by administration of
19 doxycycline; correct?

20 A. There is no indication in this abstract.

21 Q. Let's go to the next reference, the Golub, 1990
22 reference. And this is DTX-2183, if you wanted to refer to
23 that in your binder.

24 A. I have it.

25 Q. Okay. There is no mention of nitric oxide or iNOS in

Robbins - cross

1 this article; correct?

2 A. That is correct.

3 Q. And there is no mention that the patients were tested
4 for increased iNOS expression or nitric oxide production;
5 correct?

6 A. That is correct.

7 Q. And there is also no discussion as to whether or not
8 tetracycline compound or doxycycline specifically inhibits
9 iNOS expression?

10 A. There is not.

11 Q. Let's turn to the next reference, the Golub 1992
12 article at DTX-2189.

13 A. DTX-2189.

14 Q. That's correct.

15 A. Hang on a second.

16 Q. Sure.

17 A. My seems to stop at 2188. Let me look.

18 Q. Sure. I can hand one up to you.

19 A. That would be lovely, if you could.

20 MS. WILGOOS: May I approach, your Honor?

21 THE COURT: You may.

22 (Documents passed forward.)

23 BY MS. WILGOOS:

24 Q. This is an article you considered as part of your
25 opinion; correct, Dr. Robbins?

Robbins - cross

1 A. Yes, I believe so.

2 Q. And it's a review article?

3 A. I'm sorry.

4 Q. It's a review article?

5 A. It is.

6 Q. And to your knowledge, there is no new experimental
7 data that was reported in this article; is that right?

8 A. That is correct.

9 Q. Okay. And in this article, there is no mention of
10 nitric oxide production or iNOS expression?

11 A. That is correct.

12 Q. Okay. And there is also no statement in this article
13 that tetracyclines could inhibit iNOS expression or nitric
14 oxide production; correct?

15 A. That is correct.

16 Q. Let's turn to the next study, which is 2188, which I
17 think you said you have in your binder.

18 A. Yes.

19 Q. It's the Golub 1983 article. And similar to the
20 other four articles we just discussed, there is no mention
21 of nitric oxide or iNOS in this article; is that right?

22 A. I believe that is correct, yes.

23 Q. Okay. Now, let's talk about the references you
24 cited regarding rheumatoid arthritis. You are not a
25 rheumatologist; correct?

Robbins - cross

1 A. That is correct.

2 Q. Okay?

3 A. Although I will clarify, patients with especially
4 rheumatoid arthritis do get some forms of lung disease and
5 do get frequently infected, especially one on anti-TNF
6 therapy, so I do see some of these patients or I did see
7 some of these patients in my former role as a pulmonary
8 critical care physician.

9 Q. But you are not considered an expert in rheumatoid
10 arthritis?

11 A. I would not be.

12 Q. For purposes of this litigation, you have not formed
13 an opinion as to whether or not 40 milligrams of doxycycline
14 administered once daily would be an effective treatment for
15 rheumatoid arthritis; is that right?

16 A. That is correct.

17 Q. And you also have not formed an opinion as to whether
18 or not 20 milligrams of doxycycline twice a day would be
19 effective to treat rheumatoid arthritis; is that right?

20 A. That is correct.

21 Q. And you do not have any opinion regarding whether or
22 not 20 milligrams of doxycycline administered twice a day
23 inhibits endogenous production of inducible nitric oxide
24 synthase in patients with rheumatoid arthritis?

25 A. That is correct.

Robbins - cross

1 Q. Similarly, you do not have an opinion regarding
2 whether 20 milligrams of doxycycline twice a day inhibits
3 endogenous production of nitric oxide in patients with
4 rheumatoid arthritis; correct?

5 A. That is correct.

6 Q. Now, rheumatoid arthritis has been proposed to be an
7 infectious disease; correct?

8 A. Yes, it has.

9 Q. Okay. Let's talk about another reference that you
10 cited in your direct exam, the Greenwald 1994 reference,
11 which is at DTX-2184 that we cited to you in your direct
12 exam.

13 A. Yes.

14 Q. Okay. There is no mention of nitric oxide or iNOS in
15 this paper; correct?

16 A. That is correct.

17 Q. And there is no indication in this paper as to
18 whether or not the patients treated had elevated levels of
19 iNOS activity prior to or during the study; is that right?

20 A. That is correct.

21 Q. Okay. There is also no indication in this paper as
22 to whether or not the patients treated had elevated levels
23 of nitric oxide production activity prior to or during the
24 trial?

25 A. In this paper, that is correct.

Robbins - cross

1 Q. Okay. And there is no report in this paper that
2 tetracycline decreased iNOS expression or nitric oxide
3 production in any of these patients; is that right?

4 A. No, there is not. Yes, that is correct.

5 Q. Just for clarification, there is nothing in the
6 report that tetracycline decreased the iNOS expression or
7 nitric oxide production in any of these patients. That's
8 correct, right?

9 A. Yes.

10 Q. Let's talk about the next reference, Greenwald 1987,
11 which is DTX-2186. Do you have that one?

12 A. Yes.

13 Q. This article does not mention inducible nitric oxide
14 synthase or nitric oxide; is that true?

15 A. That is correct.

16 Q. And there is no disclosure in this article as to
17 whether the patients that were treated with minocycline
18 experienced any increased iNOS activity or NO production as
19 part of their rheumatoid arthritis condition; correct?

20 A. That is correct.

21 Q. Let's go to what I think is our last reference here,
22 the Tilley 1995 article. Sorry. It's DTX-2187, if you
23 wanted to look at that.

24 A. Okay. Thank you.

25 Q. Do you have that?

Robbins - cross

1 A. I do.

2 Q. The Tilley reference does not mention nitric oxide;
3 correct?

4 A. It does not.

5 Q. Or iNOS?

6 A. It does not.

7 Q. Let's take a look at page 81 of the reference, the
8 first paragraph in the right-hand column. It says a small
9 one year clinical trial comparing tetracycline,
10 250 milligrams per day with placebo could not show
11 significant benefit in patients with rheumatoid arthritis.

12 You have read the article that is referenced
13 there; correct?

14 A. Where is this again?

15 Q. Sure. It's actually up on the screen, if you wanted
16 to look there. This is in the first column of the Tilley
17 article. Sorry. The right-hand column of the first page
18 the last sentence.

19 A. A small one year clinical trial comparing
20 tetracycline, 250 milligrams per day with placebo could not
21 show significant benefit in patients with rheumatoid
22 arthritis. It references the number 5, yes.

23 Q. Yes. And have you read that reference number five,
24 right? It's the Skinner 1971 report.

25 A. Probably. I can't recall off the top of my head but

Robbins - cross

1 it's likely I did.

2 Q. Do you recall testifying at your deposition you are
3 familiar with that paper?

4 A. I do not recall testifying at my deposition with that
5 paper, but it's likely that I have. It's likely that I have
6 read it. I cannot remember it well at the moment.

7 Q. You would agree that this trial, the Skinner trial,
8 using 250 milligrams per day of doxycycline did not show
9 significant benefit; correct?

10 MR. REED: Objection, your Honor,
11 mischaracterizes.

12 THE COURT: Mischaracterizes what?

13 MR. REED: It's tetracycline.

14 MS. WILGOOS: I apologize. I'll restate the
15 question.

16 BY MS. WILGOOS:

17 Q. You would agree, Dr. Robbins, that this trial, the
18 Skinner trial referenced in Tilley using 250 milligrams per
19 day of tetracycline did not show significant benefit;
20 correct?

21 A. According to the sentence there, that is correct, and
22 I have no reason to dispute it.

23 Q. Okay. Let's take a look at page 87 of the Tilley
24 article, discussing the conclusions of the article.

25 On page 87, Tilley states, whether the

Robbins - cross

1 antirheumatic activity of minocycline is mediated by its
2 antimicrobial, antiinflammatory or immunoregulatory
3 properties remains to be determined.

4 Do you see that statement?

5 A. Yes, I do.

6 Q. And you have no reason to disagree with that
7 statement either; correct?

8 A. Based on the finding in this article, that is
9 correct. I would have no reason to disagree with that.

10 Q. Okay. You think it's a fair statement.

11 In 1996, many people involved in both clinical
12 and nitric oxide research would have been excited to have a
13 relatively specific iNOS inhibitor; correct?

14 A. That is correct.

15 Q. Nitric oxide can be reduced by inhibiting expression
16 of the iNOS gene; correct?

17 A. If the iNOS gene is up-regulated and conditioned,
18 nitric oxide should be reduced by inhibiting, correct.

19 Q. Okay. And you would agree that tetracycline
20 compounds, including doxycycline, can inhibit nitric oxide
21 production?

22 A. Given the caveat that they're given a sufficient
23 dosage, yes, or high enough concentrations, yes.

24 Q. Okay. I'm asking you specifically about the
25 compound. Tetracycline compounds, including

Robbins - cross

1 doxycycline, can inhibit nitric oxide production; is that
2 correct?

3 A. Yes, they can.

4 Q. Okay. And that is something, data from your own
5 laboratory showed that; right?

6 A. That's correct. We showed that with doxycycline.

7 Q. Okay. As well as data in the Amin patents and other
8 experimental data of the Amin inventor showed that as well;
9 correct?

10 A. That is correct.

11 Q. And doxycycline decreases NO production from iNOS by
12 destabilizing iNOS mRNA; correct?

13 A. Our data would seem to indicate that. Yes, correct.

14 Q. Okay. And just to clarify something you said
15 earlier, you believe that the ability of tetracycline
16 compounds to inhibit nitric oxide production and iNOS
17 expression in humans is dose dependent. Is that your
18 testimony?

19 A. I think that the compound probably has to be in the
20 body in sufficient amounts to inhibit the nitric oxide
21 production, yes.

22 Q. Okay. Now, you're not aware of any reports in the
23 literature prior to August of 1996 that tetracyclines had
24 any effect on iNOS; correct?

25 A. That is correct.

1 Q. All right. And you are not aware of any reports in
2 literature prior to August of 1996 that tetracyclines had
3 any effect on nitric oxide; is that correct?

4 A. That is correct.

5 Q. Okay.

6 THE COURT: Ms. Willgoos, we've reached that
7 time together.

8 MS. WILLGOOS: Two more questions.

9 THE COURT: Then you can have them.

10 MS. WILLGOOS: Thank you.

11 BY MS, WILLGOOS:

12 Q. To your knowledge, there is no publication prior to
13 the Amin patents that tetracyclines inhibit nitric oxide; is
14 that right?

15 A. That is correct.

16 Q. Or iNOS expression?

17 A. That is correct.

18 MS. WILLGOOS: I'm finished, your Honor.

19 THE COURT: Thank you.

20 MR. REED: We're done. No redirect.

21 THE COURT: You're done. No redirect?

22 MR. REED: No.

23 THE COURT: Fine. We will begin tomorrow at
24 9:00 o'clock, but until then, we'll be in recess. See you
25 in the morning.

1 MS. WILLGOOS: Thank you, your Honor.

2 (Court recessed at 6:00 p.m.)

3

4 I hereby certify the foregoing is a true and accurate
5 transcript from my stenographic notes in the proceeding.

6

7 /s Brian P. Gaffigan
8 Official Court Reporter
9 U.S. District Court

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25